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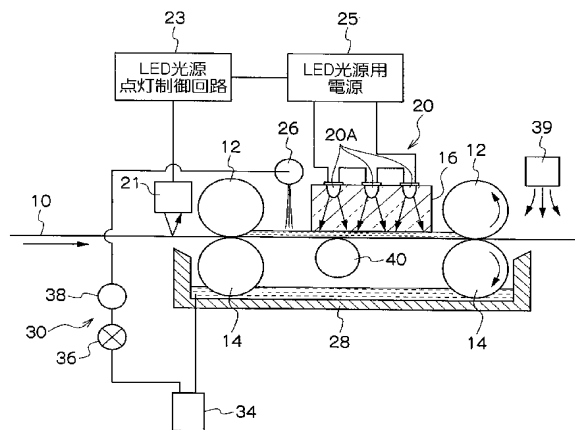
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(54) Title: METHOD FOR POST-EXPOSURE OF PLANOGRAPHIC PRINTING PLATE, POST-EXPOSURE APPARATUS, EXPOSURE APPARATUS, UNIT FOR EXPOSURE, IMAGE-DEVELOPING METHOD, AND IMAGE-DEVELOPING APPARATUS

(54) 発明の名称: 平版刷版の後露光方法、後露光装置、露光装置、露光用器具、現像方法、及び現像装置



23... LED LIGHT SOURCE ILLUMINATION-CONTROLLING CIRCUIT
25... ELECTRICAL POWER SOURCE FOR LED LIGHT SOURCE

(57) Abstract: The object is to enable the exposure of a planographic printing plate with a small amount of light while preventing the occurrence of inhibition of radical photopolymerization by oxygen. After an image-developing treatment, an image-recording layer remains on the surface of a planographic printing plate (10) so as to form an image on the surface of the planographic printing plate (10). The surface of the image-recording layer is covered with a liquid layer so that the entrance of oxygen can be blocked. In this state, the entire surface of the image-recording layer is exposed to light having such a wavelength that radical photopolymerization can occur. The entire surface of the image-recording layer which forms an image can be polymerized and cured by completely proceeding radical polymerization without being affected by the inhibition of polymerization by oxygen. In this manner, the printing durability of the planographic printing plate (10) can be improved. By exposing to light while blocking the entrance of oxygen, a high sensitivity can be achieved.

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(57) 要約: 酸素によるラジカル光重合の阻害を防止して少ない光量で平版刷版の露光を行うことを可能とする。
現像処理されて平版刷版10の表面に画像を形成するように残っている画像記録層の上を液体の層で覆って酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光で全面露光を行う。酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進めるようにして、画像を形成している画像記録層全体をポリマー化して硬化して、平版刷版10の耐刷性を向上する。酸素を遮断する状態で露光して、高感度化を図る。

明 細 書

平版刷版の後露光方法、後露光装置、露光装置、露光用器具、現像方法、及び現像装置

技術分野

[0001] この発明は、平板状の支持体の表面にラジカル光重合によって潜像を記録するための画像記録層を設けた平版刷版に対して露光処理、現像処理をした後に、画像記録層表面に酸素遮断層が無い状態で光重合層硬化処理を行うための平版刷版の後露光方法、後露光装置、露光装置、露光用器具、現像方法、及び現像装置に関する。

背景技術

[0002] 一般に、平版刷版の作成方法では、支持体上に光重合性の感光膜(画像記録層)を設けた平版刷版の原版の感光膜を、露光装置で露光して重合反応を起こさせる。これによって、画像部を固化させた潜像を形成する。その後、平版刷版の潜像が形成された感光膜における重合されなかった非画像部を、現像液で除去して平版刷版を作成する。このような方法が広く行なわれている。

[0003] 近年、平版印刷の分野では、直接平版刷版を製版するCTP(Computer to Plate)システムが実用化されている。このシステムでは、未露光の平版刷版の供給を受ける。この平版刷版に対し、画像データをコンピュータ処理することで光源のレーザー光が直接変調されたレーザー光を投影して平版刷版の原版の画像記録層に直接画像を記録するレーザー露光処理をする。自動現像機で感光性平版刷版上に形成された潜像を顕像に変換する現像処理をする。

[0004] このようなCTPシステムで利用するために、レーザー光を直接照射することにより高感度で微細な露光が可能である、ラジカル連鎖重合反応を利用したレーザー対応の平版刷版の開発が進んでいる。

[0005] このラジカル連鎖重合反応を利用したレーザー対応の平版刷版に対する露光処理では、画像記録層に対してレーザー光によって露光して画像記録層の露光した領域でラジカル重合反応を生じさせることにより画像記録層をポリマー化して硬化させる。

- [0006] この露光処理においては、空気中の酸素が、露光により発生した画像記録層中のラジカルを失活化させる。この作用は、ラジカル重合反応を妨げる要因になっている。このため、平版刷版は、画像記録層の露光された領域で空気中の酸素によりラジカル重合反応を妨げられることにより感度が低下する。よって、ある程度以上に高感度化することが困難である。
- [0007] そこで、平版刷版では、アルミ支持体上に形成された画像記録層の上にPVA(ポリビニルアルコール)などのオーバーコート層を形成して空気中の酸素を遮断する。このように空気中の酸素が画像記録層内に入り込まないようにして高感度化を図っている。
- [0008] 従来、上述のようなラジカル光重合によって潜像を記録する画像記録層が設けられた平版刷版を製版する際に、耐刷性を向上させるための平版刷版の製版方法や後露光装置が提案されている(例えば、特許文献1、特許文献2、特許文献3、特許文献4及び特許文献5参照)。これらでは、露光・現像の処理後に後露光処理し、又は加熱処理することにより、現像後の平版刷版に形成された顕像部分をさらに重合させて硬化させている。
- [0009] しかし、このような後露光処理を行う平版刷版の製版方法や後露光装置では、現像又は現像前処理の段階で、オーバーコート層が除去されている。そのため、平版刷版に対して後露光を行う際に、露光により発生した画像記録層中のラジカルを失活化させる作用をもつ空気中の酸素が画像記録層内に入り込む。酸素による重合阻害の影響を大きく受けることになる。
- [0010] このため、十分な後露光効果を得る為には、後露光装置に非常に照度が高い大型の光源を装着しなければならず、後露光装置が大型化するという問題があった。
- [0011] さらに、例えば、後露光装置に装着する照度が高い光源として水銀ランプを用いた場合には、水銀ランプに電力を供給する高圧電源が必要である。さらに、水銀ランプの点灯後輝度が安定するまでに時間がかかる。このため、電源投入後処理可能となるまでに5～10分の待機時間が必要となり作業効率が低下する。また、待機時間程度の間隔で断続的に平版刷版が後露光装置に搬入されて来る場合でも、常に水銀ランプを点灯しておかなければならない。よって、水銀ランプの寿命が尽きて交換す

るまでの期間が短くなるという問題がある。

- [0012] また、後露光を行う大型の装置部分を組み込んで一体化した平版刷版の現像装置を実現させることが困難であった。さらに、後露光処理を行わない平版刷版の現像装置だけで製版された平版刷版が十分な耐刷性能を得るようには、平版刷版を露光処理するときの露光エネルギーを高くしなければならない。このため、露光装置に高出力の大型で高価な光源装置を用いる必要がある。
- [0013] 一方、平版刷版に酸素遮断用オーバーコート層を設けて高感度化した場合には、露光後の現像工程などにおいて、オーバーコート層を溶解除去する必要がある。PV Aは水溶性である。そのため、現像工程での現像液にオーバーコート層が溶け込んで固形成分として固まることがある。また、現像液にオーバーコート層が溶解せず固形成分として残留することがある。これらにより、印刷機の内部が汚染されたりして、印刷物の汚れを発生させる虞がある。
- [0014] 従来、上述のような問題を解決する手段として、感度を保持すると共に現像液にオーバーコート層の固形成分が残留して不具合が生じることを解消する手段が提案されている(例えば、特許文献6参照)。ここでは、エチレン性不飽和結合を有する化合物と光重合開始剤とを含有する光重合性層が設けられた印刷版原版を露光するにあたり、酸素による反応阻害を抑制するために、オーバーコート層(酸素遮断性層)に代えて、印刷版原版よりも大きな透明シートが重ね合わされる。加えて、酸素の希薄な環境を実現すること及びシートの密着性を得るために、印刷版原版に大きな透明シートを被せたものが複数の吸引孔を有する部材上に配置され、この吸引孔より排気を行ないながら像露光する。
- [0015] しかし、このような印刷版原版に大きな透明シートを被せた状態で露光処理する手段では、柔軟な透明シートを印刷版原版に被せ、この透明シートを通して露光処理を行っている。このため、透明シートを何度も使用すると、透明シートに汚れやゴミが付着したり、透明シートに傷や皺が発生したりする。これらによって露光ビームが拡散されて露光不良が発生するという問題がある。
- [0016] この問題を回避する為には、露光処理を行う毎に、新たな透明シートに交換することが必要となり、処理費用が嵩むことになる。さらに、露光処理を行う毎に、新たな透

明シートに交換する場合には、露光処理を行う毎に透明シートを感材面に重ねるという作業工程が必要となり、生産性が低下する。

特許文献1:特開2001-48326号公報

特許文献2:特開2001-51426号公報

特許文献3:特開2001-159811号公報

特許文献4:特開平11-265069号公報

特許文献5:特開2002-162753号公報

特許文献6:特開平9-197655号公報

発明の開示

発明が解決しようとする課題

[0017] 本発明は、上述の問題に鑑み、十分な耐刷性能を有する平版刷版を製版可能なように、平版刷版の現像処理後に後露光処理を行う際に、空気中の酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態にして所要の少ない光量で全面露光を行うことにより後露光処理をできると共に、後露光処理に必要な波長の光を出射して均一に照明でき、しかも平版刷版に対する後露光処理を行うときにのみ点灯して待機時間無しで後露光処理を開始できるため寿命が尽きて交換するまでの期間を長くできる光源が利用可能である平版刷版の後露光方法、後露光装置、現像装置、及び現像方法を新たに提供することを目的とする。

[0018] また、本発明は、上述の問題に鑑み、平版刷版に露光処理を行う際に空気中の酸素を遮断することにより空気中の酸素が画像記録層内に入り込まないようにして、平版刷版の画像記録層を高感度化した状態で、効率良く作業できるようにした平版刷版の露光装置及び露光用器具を新たに提供することを目的とする。

課題を解決するための手段

[0019] 本発明の請求項1に記載の平版刷版の後露光方法は、支持体の表面にラジカル光重合反応によって潜像が形成される画像記録層を有する平版刷版に対して、画像に対応した露光用の光を照射してラジカル光重合反応を起こさせることにより画像部を固化させた潜像を形成し、平版刷版の潜像が形成された画像記録層におけるラジカル光重合されなかった非画像部を除去する現像処理をし、現像処理されて平版刷

版の表面に画像を形成するように残っている画像記録層の上を液体の層で覆って酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光で全面露光を行うことにより後露光処理をする。

[0020] 上述の後露光方法によれば、現像処理されて平版刷版の表面に画像を形成するように残っている画像記録層の上を液体の層で覆って酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光を液体の層を通して照射することにより全面露光を行う。これにより、酸素によるラジカル光重合の阻害を防止して、少ない光量で十分なラジカル光重合反応を得られる。そのため、後露光処理に必要な波長の光を出射して均一に照明でき、平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため光源の寿命が尽きて交換するまでの期間を長くできる。

[0021] 本発明の請求項2に記載の平版刷版の後露光装置は、板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層を形成した平版刷版に対する露光処理で画像に対応した露光用の光を照射して画像部を固化させた潜像を形成し、平版刷版に対する現像処理で潜像が形成された画像記録層におけるラジカル光重合されなかった非画像部を除去した平版刷版に対して光重合層硬化処理を行う、平版刷版の耐刷性向上用の後露光装置において、平版刷版を気体中で搬送する搬送路と、搬送路上を搬送されている平版刷版の表面に画像を形成するように残っている画像記録層の上に、酸素を遮断するため、平版刷版に対して不活性で画像記録層にラジカル光重合を起こさせる波長の光を透過可能な液体の層を作るための液体供給ユニットと、搬送路上を搬送されている平版刷版の全面に対して、液体の層を通してラジカル光重合を起こさせる波長の光を照射する光照射ユニットと、を有する。

[0022] 上述のように構成することにより、平版刷版が気体中で搬送する搬送路上を搬送されている状態で、現像処理されて平版刷版の表面に画像を形成するように残っている画像記録層の上を液体の層で覆った状態で後露光用の光を全面に照射する。これにより、酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進めるようにして、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版の耐刷性を向上することができる。さらに、酸素を遮断する状態で、ラジカル光

重合を起こさせる波長の光を液体の層を通して照射することにより全面露光を行う。これにより、酸素によるラジカル光重合の障害を防止して、少ない光量で十分なラジカル光重合反応を得られる。そのため、後露光処理に必要な波長の光を出射して均一に照明できて、平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため、光源の寿命が尽きて交換するまでの期間を長くでき、廉価な平版刷版の耐刷性向上用の後露光装置を提供できる。

[0023] 請求項3に記載の発明は、請求項2に記載の平版刷版の後露光装置において、光照射ユニットが、発光ダイオード(LED)を有する。

[0024] 上述のように構成することにより、請求項2に記載の発明の作用、効果に加えて、LEDは点灯後直ちに所定の光量で発光する特性があるので、通電してから所定の発光量に至るまで長い待機時間を要する他の光源と異なり、後露光処理に必要なときだけ点灯させることができる。よって、平版刷版に対して後露光処理を行うときだけLEDを点灯するように制御することにより、後露光処理をしていないときにLEDを点灯するようなエネルギーの無駄を省き、後露光装置でLEDを使用できる期間(後露光装置で使用されているときのLEDの使用寿命)を長くすることができる。しかもLEDは廉価であるので、これを用いた平版刷版の耐刷性向上用の後露光装置を廉価に製造することができる。

[0025] 本発明の請求項9に記載の平版刷版の露光装置は、板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層を形成した平版刷版を、画像記録層の表面に酸素遮断層が無い状態で露光用の光ビームを照射する露光位置に搬入して露光処理を行う平版刷版用の露光装置であって、平版刷版を気体中で搬送する搬送路と、搬送路における露光位置に搬送される平版刷版の表面から液体を介在させる間隔を開けて配置される、透明な部材に露光用の光ビームを透過させる平面が形成された露光補助部材と、搬送路上における露光補助部材の搬送方向上流側で、露光補助部材と平版刷版との間に平版刷版に対して不活性で露光用の光ビームを透過可能な液体を充填させるようにする液体供給ユニットと、を有する。

[0026] 上述のように構成することにより、平版刷版が気体中で搬送する搬送路上を搬送されている状態で、平版刷版の画像記録層を液体で被って、露光用の光ビームを照射

する際に画像記録層を空気中の酸素から遮断された状態とする。これにより、画像記録層において、酸素による重合阻害が発生することなく効率よくラジカル重合反応を進め、良好にポリマー化して潜像を形成できる。さらに、平版刷版を気体中で搬送する搬送路上を搬送するものであるので平版刷版の裏側を液体で濡らす必要がない。そのため、必要最小限の液体を用いて効率良く画像記録層を酸素から遮断することができ、また、この液体中に塵が混入する確率を下げ、この液体中に浮遊する塵による露光欠陥の発生を抑制できる。

- [0027] 請求項10に記載の発明は、請求項9に記載の平版刷版の露光装置において、露光補助部材と、平版刷版との距離を、平版刷版上に生じる液体の層の厚さ以下に設定している。
- [0028] 上述のように構成することにより、請求項9に記載の発明の作用、効果に加えて、露光補助部材と平版刷版との間に、液体の層だけが入り込むようにして、液体の層に空気が混入することを防止できる。
- [0029] 請求項11に記載の発明は、請求項9又は請求項10に記載の平版刷版の露光装置において、搬送路上に配置された露光補助部材の下方に対応した位置に、平版刷版の下面をガイドするガイド部材を配置している。
- [0030] 上述のように構成することにより、請求項9又は請求項10に記載の発明の作用、効果に加えて、搬送されている平版刷版の振動を抑え、平版刷版の画像記録層に常に適切に合焦した状態で露光処理することができる。
- [0031] 請求項12に記載の発明は、請求項9乃至請求項11の何れか1項に記載の平版刷版の露光装置において、液体供給ユニットが、搬送路上における露光補助部材から直近の搬送方向上流側に配置されて、平版刷版に転接する搬送ローラと、搬送ローラに対して液体を流下する液体シャワーバーと、液体シャワーバーから流下した液体を導入ガイド部で受け、搬送ローラの外周面と円弧状のガイド部分との間に導入し、これらの間を流して平版刷版上へ導くように構成した流下ガイド部材と、を有する。
- [0032] 上述のように構成することにより、請求項9乃至請求項11の何れか1項に記載の発明の作用、効果に加えて、搬送路上における露光補助部材と、これより直近の搬送方向上流側に配置された搬送ローラとの間の距離を、液体シャワーバーを配置する

ためのスペース分だけ短く構成して、装置本体を小型化することができる。

[0033] 本発明の請求項13に記載の露光用器具は、搬送される平板状の被露光体に対し、被露光体の表面を空気から遮断する液体の層を介して透明な部材部分を配置し、露光用の光ビームが透明な部材部分と液体の層とを透過して被露光体に照射するようにするための露光用器具であって、透明な部材部分の底面における、被露光体の搬送方向上流側に当たる端部で被露光体の搬送方向に直交する方向に渡る位置に、液体供給用開口を配設し、透明な部材部分の外部から送給された液体を、液体供給路を通して液体供給用開口から、露光用器具の透明な部分の底面と被露光体との間に供給するように構成したことを特徴とする。

[0034] 上述のように構成することにより、被露光体が空気中で搬送する搬送路上を搬送されているときに、被露光体の表面を液体が被って空気から遮断された状態となる。これにより、空気中の成分による障害が発生することなく効率よく潜像を形成可能とする。さらに、液体供給用開口が、露光用器具の透明な部分にある。これにより、少ない液体の供給量で、被露光体の表面と露光用器具の透明な部分との間に液体を十分に充填することができる。

[0035] 本発明の請求項14に記載の平版刷版の現像方法は、支持体の表面上に光ラジカル重合反応を利用した画像形成のための画像記録層を設けた平版刷版の現像方法において、画像記録層に画像に対応した露光用の光を照射して潜像が形成された平版刷版に対して、潜像が形成された画像記録層の未露光の部分的支持体から除去して潜像を顕在化する現像処理をし、現像処理された平版刷版の少なくとも画像記録層上に液体を供給して現像液を洗浄すると共に、画像記録層の表面を液体で覆った酸素遮断状態で光ラジカル重合反応を開始又は促進する波長の光で全面露光することにより、平版刷版の耐刷性を向上する後露光処理を行う後露光処理をする。

[0036] 上述の平版刷版の現像方法によれば、現像処理されて平版刷版の表面に画像を形成するように残っている画像記録層に付着している現像液を洗浄するための液体で洗い流す処理を行うときに、この現像液を洗浄するための液体の層で画像記録層の表面を覆って酸素を遮断する状態とし、この画像記録層の表面を酸素が遮断され

るように覆っている液体の層を通してラジカル光重合を起こさせる波長の光を照射することにより全面露光を行う。これにより、酸素によるラジカル光重合の阻害を防止して少ない光量で十分なラジカル光重合反応を得られる。よって、後露光処理に必要な波長の光を出射して均一に照明できて平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため光源の寿命が尽きて交換するまでの期間を長くできる。さらに画像記録層に付着している現像液を液体で洗い流すための構成と、画像記録層の表面を酸素が遮断されるように液体の層で覆うための構成とを共用することにより、構成を簡素化できる。

[0037] 本発明の請求項15に記載の平版刷版の現像装置は、板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層が形成された平版刷版に、露光用の光が照射されて画像記録層に潜像が形成された平版刷版を搬入して、画像記録層における露光されなかった部分を支持体から除去して画像を顕在化する現像部と、画像が顕在化された平版刷版を気体中で搬送する搬送路と、搬送路上を搬送されている平版刷版に対して、少なくとも表面に画像を形成するように残っている画像記録層の上に付着している現像液を洗い流すと共に、画像記録層にラジカル光重合を起こさせる波長の光を透過可能な酸素を遮断する層を作るように、液体を供給する液体供給ユニットと、搬送路上を搬送されている平版刷版の画像記録層全面に対して、液体の層を通してラジカル光重合を起こさせる波長の光を照射する光照射ユニットと、を有する。

[0038] 上述のように構成することにより、平版刷版が気体中で搬送する搬送路上を搬送されている状態で、液体供給ユニットにより、平版刷版の画像記録層上に洗浄用の液体を供給して現像液を洗い流すと共に、現像処理されて平版刷版の表面に画像を形成するように残っている画像記録層の上を洗浄用の液体の層で覆った状態で光照射ユニットから後露光用の光を全面に照射する。これにより、酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進めるようにして、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版の耐刷性を向上することができる。さらに、酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光を液体の層を通して照射することにより全面露光を行う。これにより、酸素によるラジカル

光重合の阻害を防止して、少ない光量で十分なラジカル光重合反応を得られる。このため、後露光処理に必要な波長の光を出射して均一に照明できて平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため、光源の寿命が尽きて交換するまでの期間を長くできる。さらに液体供給ユニットが、画像記録層に付着している現像液を液体で洗い流すための構成と、画像記録層の表面を酸素が遮断されるように液体の層で覆うための構成とを共用する。これにより、構成を簡素化して、廉価な平版刷版の現像装置を提供できる。

[0039] 本発明の請求項17に記載の平版刷版の現像方法は、支持体の表面上に光ラジカル重合反応を利用した画像形成のための画像記録層が設けられた平版刷版の現像方法において、画像記録層に画像に対応した露光用の光が照射されて潜像が形成された平版刷版に対して、潜像が形成された画像記録層の未露光の部分和支持体から除去して潜像を顕在化する現像処理工程と、現像処理工程を終えた平版刷版の表面に画像を形成するように残っている画像記録層の上を、親水層を保護する保護層を形成するために塗布したガム液の層で覆ってガム液の溶媒を含む成分が酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光で全面露光を行うことにより平版刷版の耐刷性を向上させる保護層形成工程及び後露光処理工程を有する。

[0040] 上述の平版刷版の現像方法によれば、現像処理されて平版刷版の表面に画像を形成するように残っている画像記録層における親水層を保護する保護層を形成するためにガム液を塗布してから、平版刷版の表面を層状になって覆っているガム液を乾燥させる。乾燥するとき、画像記録層の表面を層状になって覆っているガム液の溶媒を含む成分が酸素を遮断する状態で、このガム液の層を通してラジカル光重合を起こさせる波長の光を照射することにより全面露光を行う。これにより、酸素によるラジカル光重合の阻害を防止して少ない光量で十分なラジカル光重合反応を得られる。よって、後露光処理に必要な波長の光を出射して均一に照明できて、平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため、寿命が尽きて交換するまでの期間を長くできる、少ない光量で発光する光源を利用することができる。さらに画像記録層に保護層を形成するための構成と、画像記録

層の表面を酸素が遮断されるように覆うための構成とを共用することにより、構成を簡素化できる。

[0041] 本発明の請求項18に記載の平版刷版の現像装置は、板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層を形成した平版刷版に、露光用の光が照射されて画像記録層に潜像が形成された平版刷版を搬入して、画像記録層における露光されなかった部分を支持体から除去して画像を顕在化する現像部と、画像が顕在化された平版刷版を気体中で搬送する搬送路と、搬送路上を搬送されている平版刷版に対して、少なくとも表面に画像を形成するように残っている画像記録層の上に親水層を保護する保護層を形成するためのガム液を塗布し、ガム液の溶媒を含む成分が画像記録層にラジカル光重合を起こさせる波長の光を透過可能であると共に酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態で、搬送路上を搬送されている平版刷版の画像記録層全面に対してラジカル光重合を起こさせる波長の光を照射する光照射ユニットと、を有する。

[0042] 上述のように構成することにより、平版刷版が気体中で搬送する搬送路上を搬送されているときに、少なくとも画像が形成された画像記録層の上にガム液を塗布してガム液の層で覆い、このガム液の溶媒を含む成分が画像記録層にラジカル光重合を起こさせる波長の光を透過可能で酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態で、光照射ユニットから後露光用の光を全面に照射する。酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進めて、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版の耐刷性を向上することができる。さらに、酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光を液体の層を通して照射することにより全面露光を行う。これにより、酸素によるラジカル光重合の阻害を防止して、少ない光量で十分なラジカル光重合反応を得られる。そのため、後露光処理に必要な波長の光を出射して均一に照明できて、平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため、寿命が尽きて交換するまでの期間を長くできる、少ない光量を発光する光源を利用できる。さらに画像記録層に保護層を形成するための構成と、画像記録層の表面を酸素が遮断されるように覆うための構成とを共用するので、構成を簡素化し

て、廉価な平版刷版の現像装置を提供できる。

発明の効果

- [0043] 本発明の平版刷版の後露光方法及び装置によれば、平版刷版の現像処理後に後露光処理を行う際に、空気中の酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態にして所要の少ない光量で全面露光を行うことにより後露光処理ができる。これにより、耐刷性向上ができる。また、発光する光量が少ないが平版刷版の後露光処理に必要な波長の光を出射して均一に照明でき、しかも平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため、寿命が尽きて交換するまでの期間を長くできる小型で廉価な光源を用いることができる。このため、後露光装置を小型で廉価にできるという効果がある。
- [0044] 本発明の平版刷版の露光装置及び露光用器具によれば、平版刷版に露光処理を行う際に空気中の酸素を遮断することにより空気中の酸素が画像記録層内に入り込まないようにして、平版刷版の画像記録層を高感度化した状態で、効率良く作業できるという効果がある。
- [0045] 本発明の平版刷版の現像方法及び装置によれば、平版刷版の現像処理後の後露光工程で、空気中の酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態にして所要の少ない光量で全面露光を行う。これにより、十分な耐刷性能を有する平版刷版を製版できる。発光する光量が少ないが平版刷版の後露光処理に必要な波長の光を出射して均一に照明でき、しかも平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため寿命が尽きて交換するまでの期間を長くできる小型で廉価な光源を用いることができる。このため、小型で廉価な平版刷版の現像装置を製作可能とするという効果がある。
- [0046] 本発明の平版刷版の現像方法及び装置によれば、平版刷版に対して露光処理、現像処理をした後、親水層を保護する為いわゆるガム液を塗布した後に乾燥させて画像記録層表面に親水層の保護層を形成する工程において、塗布したガム液による酸素を遮断する機能を利用して空気中の酸素が画像記録層内に入り込まない状態にする。これにより、所要の少ない光量で全面露光する後露光処理を実行する。このため、十分な耐刷性能を有する平版刷版を製版できる。発光する光量が少ないが

平版刷版の後露光処理に必要な波長の光を出射して均一に照明でき、しかも平版刷版に対する後露光処理を行うときにのみ点灯し待機時間無しで後露光処理を開始できるため寿命が尽きて交換するまでの期間を長くできる小型で廉価な光源を用いることができる。このため、小型で廉価な平版刷版の現像装置を製作可能とするという効果がある。

図面の簡単な説明

[0047] [図1]本発明の第1実施の形態に係わる平版刷版の後露光装置の概略構成を示す斜視図である。

[図2]本発明の第1実施の形態に係わる平版刷版の後露光装置を部分断面で示す概略構成図である。

[図3]本発明の第2実施の形態に係わる平版刷版の後露光装置を部分断面で示す概略構成図である。

[図4]本発明の第2実施の形態に係わる平版刷版の後露光装置に用いる後露光用器具を取り出して示す斜視図である。

[図5]本発明の第2実施の形態に係わる平版刷版の後露光装置に用いる後露光用器具を取り出して示す分解斜視図である。

[図6]本発明の第3実施の形態に係わる平版刷版の後露光装置を部分断面で示す概略構成図である。

[図7]本発明の第4実施の形態に係わる平版刷版の露光装置の概略構成を示す斜視図である。

[図8]本発明の第4実施の形態に係わる平版刷版の露光装置を部分断面で示す概略構成図である。

[図9]本発明の第5実施の形態に係わる平版刷版の露光装置を部分断面で示す概略構成図である。

[図10]本発明の第6実施の形態に係わる平版刷版の露光装置を部分断面で示す概略構成図である。

[図11]本発明の第6実施の形態に係わる平版刷版の露光装置の要部を取り出して部分断面で示す拡大概略構成図である。

[図12]本発明の第7実施の形態に係わる後露光処理部を兼ねた水洗部の概略構成を示す斜視図である。

[図13]本発明の第7実施の形態に係わる後露光処理部を兼ねた水洗部を部分断面で示す概略構成図である。

[図14]本発明の第7実施の形態に係わる後露光処理部を兼ねた水洗部の他の構成例を部分断面で示す概略構成図である。

[図15]本発明の第7実施の形態に係わる後露光処理部を兼ねた水洗部のさらなる他の構成例を部分断面で示す概略構成図である。

[図16]本発明の第7実施の形態に係わる前処理部を示す概略構成図である。

[図17]本発明の第7実施の形態に係わる現像処理部を示す概略構成図である。

[図18]本発明の第8実施の形態に係わる保護層形成及び後露光処理部の要部概略構成を示す斜視図である。

[図19]本発明の第8実施の形態に係わる保護層形成及び後露光処理部の要部を部分断面で示す概略構成図である。

[図20]本発明の第8実施の形態に係わる他の構成例の保護層形成及び後露光処理部の要部を部分断面で示す概略構成図である。

[図21]本発明の第8実施の形態に係わるさらに他の構成例の保護層形成及び後露光処理部の要部を部分断面で示す概略構成図である。

[図22]本発明の第8実施の形態に係わる現像処理部を示す概略構成図である。

[図23]本発明の第8実施の形態に係わるさらに他の構成例の保護層形成及び後露光処理部に用いる搬送ローラの外周面上に液体シャワーバーからガム液を流下させるための構成の要部を取り出して示す概略構成図である。

[図24]本発明の第8実施の形態に係わる保護層形成及び後露光処理部の乾燥部に用いる後露光用の光照射ユニットを取り出して示す概略構成図である。

発明を実施するための最良の形態

[0048] まず、第1－3実施の形態について、図1－6により説明する。

[0049] 本発明の平版刷版の耐刷性向上用の後露光方法及び装置に関する第1実施の形態について、図1及び図2により説明する。

- [0050] 本実施の形態に係わる平版刷版の耐刷性向上用の後露光装置は、平板状の支持体の表面にラジカル光重合によって潜像を記録するための画像記録層が設けられた平版刷版に対して、露光処理によりポリマー化させて潜像が形成され、この後、現像処理により、現像液に浸漬した状態でブラシローラによって潜像が形成された画像記録層における未露光の部分除去して露光された画像記録層部分だけを残すことにより画像が顕在化され、この画像が顕在化された平版刷版を後露光処理するための装置として構成する。
- [0051] なお、本実施の形態に係わる後露光装置は、図示しない平版刷版の自動現像装置と別体となる独立した装置として構成し、又は自動現像装置と平版刷版を搬送するための図示しない搬送ベルトコンベヤ等を介して搬送路を接続して一体的に構成し、若しくは図示しない平版刷版の自動現像装置における現像処理後の水洗工程(洗浄工程)より後の工程に接続させるため平版刷版の自動現像装置と一体的に構成しても良い。
- [0052] 後露光装置は、大気中を搬送する搬送路上を搬送されている画像が顕在化された平版刷版10に対して、後露光処理を行う平版刷版の耐刷性向上用の装置として構成する。
- [0053] この後露光装置では、一般に用いられている光ラジカル重合反応を利用した画像形成の手段としてのフォトンモード記録方式又はヒートモード記録方式の平版刷版10で現像処理を終えたものを対象にして後露光処理を行う。
- [0054] この一般に用いられている光ラジカル重合反応を利用する平版刷版10(ラジカル重合系の平版印刷版)は、アルミニウム支持体の表面に陽極酸化皮膜を形成し、さらに陽極酸化皮膜の上に画像記録層を設けた多層構造に構成する。なお、この平版刷版10では、画像記録層の表面を覆う保護層を設けたものであっても現像処理を終えるまでに保護層が除去されているので、何ら変わりなく利用できる。
- [0055] この平版刷版10に設ける画像形成手段としての画像記録層は、光重合性材料にレーザー等の記録光によって露光することにより、ラジカル開始剤から発生したラジカルがモノマーと反応し、このモノマーがラジカル化して更にモノマーと反応を繰り返すラジカル重合反応が連鎖的に継続して起きる。これにより、大きな分子構造を有す

るポリマーとなり、このポリマーとなった部分が潜像を構成するものである。なお、画像記録層におけるレーザー記録光が当たらなかった部分は、別途行われる平版刷版10の現像処理により脱膜されて取り除かれ、ポリマーとなった部分に画像が形成される。

[0056] また、この平版刷版10では、露光処理後に現像処理することによって画像記録層におけるポリマー化した部分だけがアルミニウム支持体上に残って画像が形成される。さらに、この現像処理後の平版刷版10では、アルミニウム支持体上に画像を形成するように残っている画像記録層の部分が十分にポリマー化されているとは限らない。画像記録層の部分におけるアルミニウム支持体側の一部にポリマー化が不十分な所が残っている場合がある。

[0057] そこで、現像処理後の平版刷版10に対する後露光処理では、後露光装置によって平版刷版10の全面に画像記録層の感光領域の波長を有する光で均等に露光する。これにより、アルミニウム支持体上に画像を形成するように残っている画像記録層の部分を全体に渡って十分にポリマー化することで硬化させ、耐刷性を向上させる。

[0058] 図1及び図2に示す後露光装置では、平版刷版10を大気中で搬送する搬送路上で後露光処理を行うため、後露光位置前後の各所定位置に一对のニップローラである搬送ローラ12、14を配置する。

[0059] 各搬送ローラ12、14は、これら搬送ローラ12、14の間に平版刷版10を挟み込んだ状態で、一方の搬送ローラ12又は14を図示しない駆動源であるモータ等で回転駆動することにより、平版刷版10を搬送する。なお、これら搬送ローラ12、14は、共にフリーローラとして構成してもよい。又は、平版刷版10の表面に転接するローラだけにしてこれをフリーローラで構成し、これらの他に、平版刷版10を搬送するための駆動源で回転駆動されるニップローラを装着して構成しても良い。

[0060] 2組の搬送ローラ12、14の間に設定された後露光位置には、搬送される平版刷版10の画像記録層側の表面から所定距離(ここでは、略1mmから略3mmに設定する)をおいた位置に、透明な部材として構成された露光補助部材16を配置する。ここで、実際に実験した結果、後述するように平版刷版10上に液体供給ユニットである液体シャワーバー26によって水を供給したところ、水の表面張力の作用によって、平版

刷版10の端部に至るまで、平版刷版10の表面に平均的に広がった厚さ略1mmから略3mmの水の層ができることを確認した。

- [0061] よって、この後露光装置では、平版刷版10と露光補助部材16の底面との間に水の層だけができて空気が入り込まない状態に設定するため、液体供給ユニットである液体シャワーバー26による水の供給量を調整する。平版刷版10上にのる水の層の厚さを所定厚さとなるように制御したときに、この制御された水の層の所定厚さに等しい距離か又はこれより短い距離となるように、平版刷版10と露光補助部材16の底面との間の距離を設定する。
- [0062] この露光補助部材16は、レーザービームの入射面と出射面(底面)とを平面に仕上げた、透明なガラス又はプラスチック等の材料を矩形板状(直方体状)に形成したものである。なお、この露光補助部材16は、レンズとしての機能を持つように構成しても良い。
- [0063] この後露光装置では、上述のように構成した露光補助部材16を用いることにより、平版刷版10上にのる水の層の表面に凹凸ができていても、この水の層の表面に露光補助部材16が被さって水の層の表面を平面化できる。また、露光補助部材16は、その表面が平面であるので、この表面に入射した光を部分的な光量の偏りが起こらないように平均的に平版刷版10の画像記録層に照射させて良好に後露光処理することができる。
- [0064] この後露光装置では、露光補助部材16を介して後露光処理するために、後露光用の光照射ユニット20を設ける。この光照射ユニット20は、例えば、複数の発光ダイオード(LED、ここでは、紫外線を発光する紫外線LED)20Aを、例えば千鳥格子状等の高い密度で配置されるように集めて構成した光源であるLEDアレイ光源で構成する。発光ダイオード20Aは、平版刷版10の画像記録層にラジカル光重合反応を起こさせるのに適した感光用の波長の光(赤外線、可視光線又は紫外線等の所定の波長を有する光)を発光する。
- [0065] この後露光装置では、各LED20Aを、図1及び図2に示すように、露光補助部材16の上面部分に埋め込むようにして設置する。なお、複数のLED20Aを設けたLEDアレイ光源を、露光補助部材16と別体に構成しても良い。

- [0066] なお、光照射ユニット20は、感光用の波長の光を発光する面光源であるエレクトロルミネセンス(EL:Electro Luminescence)素子で構成しても良い。
- [0067] この後露光装置では、搬送路における露光補助部材16とこれより搬送方向上流側に配置された搬送ローラ12、14との間の所定位置に、液体供給ユニットとしての液体シャワーバー26を、搬送方向に直交する方向に向けて、平版刷版10の幅方向全体に渡る範囲に対応して配置する。
- [0068] この液体シャワーバー26は、例えば、円筒形に形成され、その平版刷版10に向けた周側面に等間隔で多数のノズル孔を列状に配置され、この液体シャワーバー26の内部に供給された液体(ここでは水)を各ノズルから噴射して平版刷版10の表面に略均等な薄膜状の液体の層を作る。なお、この液体シャワーバー26から噴射されて平版刷版10上へ供給された液体は、平版刷版10の表面を濡らすように広がり、その液体の表面張力によって略均等な薄膜状の液体の層を作る。このとき後露光装置では、前述したように、液体シャワーバー26による水の供給量を調整して、平版刷版10上にのる水の層の厚さを所定厚さとなるように制御する。
- [0069] このように平版刷版10上に作られた略均等な薄膜状の液体の層は、平版刷版10と共に搬送されて、露光補助部材16の位置に至り、露光補助部材16と平版刷版10との間を満たすように入り込む。液体の層が露光補助部材16と平版刷版10との間の隙間に空気の泡を残すことなく十分に埋め尽くした後露光処理用の酸素遮断状態を作り出す。
- [0070] なお、ここで用いる液体は、平版刷版10を後露光するための光ビームが透過可能で、かつ平版刷版10に対して不活性であり平版刷版10に濡れない溶液を用いることができる。ここでは通常の水道水を用いるが、その他に流動パラフィン、シリコンオイル等を用いることができる。
- [0071] この平版刷版10上に作られた略均等な薄膜状の液体の層は、平版刷版10と共に搬送されて露光補助部材16の位置を離れ、搬送方向下流側の搬送ローラ12、14で絞り落とされる。
- [0072] このように平版刷版10上から絞り落とされ又は平版刷版10の両側から零れ落ちた液体を受けるため、搬送路の下側には、露光位置を挟む2組の搬送ローラ12、14を

配置した所定範囲を含む一回り大きな範囲をカバーする、受け皿部材28を設置する。

- [0073] また、この受け皿部材28と、液体シャワーバー26との間には、液体循環管路30を設置する。この一連の液体循環管路30を構成する管部材32と液体シャワーバー26との間には、フィルタ34、ポンプ36及びヒータ38を配置する。
- [0074] この液体循環管路30は、受け皿部材28の底面に開口した取液口から導入した液体を、管部材32を通してフィルタ34へ送ってろ過してからポンプ36へ送る。このポンプ36は、フィルタ34側から吸引した液体を加圧してヒータ38へ送って約60℃から80℃程度(沸点未満でも良い)に加熱してから液体シャワーバー26へ供給し、液体シャワーバー26のノズルから所定の流量で噴射させる。なお、この液体循環管路30で液体シャワーバー26へ供給する液体の新液は、平版刷版10の処理量に応じて図示しない手段によって受け皿部材28に供給される。
- [0075] この後露光装置では、平版刷版10上の全面にシャワーバー26から加熱した液体を供給して液体の層で覆う。これにより、平版刷版10の画像を形成している画像記録層を加熱して、ラジカル重合反応を促進し、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の耐刷性を向上することができる。
- [0076] また、この後露光装置では、液体シャワーバー26のノズルから噴射された液体が平版刷版10に当たる受液位置の直下である平版刷版10の下側(裏側)に、ガイドローラ40を装着する。ガイドローラ40は、平版刷版10の裏面に転接して支持することにより、平版刷版10にノズルから噴射された液体が当たって振動を生じることを防止する。すなわち、このガイドローラ40を配置した場合には、液体シャワーバー26のノズルから噴射された液体を受けているときに平版刷版10に振動が生じることを抑制した状態で後露光処理することができる。
- [0077] また、この後露光装置では、搬送方向下流側に配置した搬送ローラ12、14から、搬送方向下流側に近接した位置に、平版刷版10の表面に乾燥させるため、約100℃に加熱された熱風を吹き付ける乾燥器39を配置する。
- [0078] この後露光装置では、乾燥器39から加熱された熱風を平版刷版10の画像を形成している画像記録層全面に吹き付ける。これにより、画像を形成している画像記録層

を加熱して、ラジカル重合反応を助長し、画像記録層全体をより確実にポリマー化して硬化させ、平版刷版10の耐刷性を向上させることができる。

- [0079] 図2に示すように、この後露光装置では、光照射ユニット20を構成するLEDアレイ光源のLED20Aを、後露光処理に必要なときだけ点灯させるための点灯制御ユニットを設ける。
- [0080] なお、この後露光装置で光照射ユニット20としてLED20Aを用いる場合には、LED20Aが点灯後直ちに所定の光量で発光する。これにより、通電してから所定の発光量に至るまで長い待機時間を要する他の光源と異なり、後露光処理に必要なときだけ点灯させるよう制御できる。
- [0081] すなわち、通電してから所定の発光量に至るまで長い待機時間を要する他の光源を用いる場合には、平版刷版10が露光補助部材16へ搬入される時より待機時間だけ前の時点でその他の光源を点灯させる操作を行わなければならない。このため、こまめに点灯と消灯とを繰り返す制御が困難である。よって、後露光処理に拘わらない無駄な点灯時間が増加してしまう。
- [0082] 光照射ユニット20としてのLED20A用の点灯制御ユニットは、露光補助部材16の搬送方向上流側に直近する搬送ローラ12、14より搬送方向上流側に当たる搬送路上の所定位置に、搬送されている平版刷版10の搬送方向先端と搬送方向後端とをそれぞれ検出可能であるように構成された版端検出センサ21を配置する。
- [0083] この版端検出センサ21は、例えば、反射型の光検出センサで構成され、搬送路上の検出位置に照射したセンサ光の反射光を受光して、その受光量の値を光源点灯制御回路23へ送信する。
- [0084] この光源点灯制御回路23は、平版刷版10の版端が搬送路上の検出位置を通過する際に、版端検出センサ21で受光した検出用反射光の光量に変化した時点で平版刷版10の版端を検出したと判断する。なお、この光源点灯制御回路23は、検出用反射光の光量が平版刷版10の表面に反射したときの所定の光量となった時点で平版刷版10の版端を検出したと判断するようにしても良い。
- [0085] また、この光源点灯制御回路23では、例えば、搬送路上を平版刷版10が搬送開始してから初めて版端を検出したときに、この版端を平版刷版10の搬送方向先端と

判断し、2度目に版端を検出したときに、この版端を平版刷版10の搬送方向後端と判断する。

[0086] この光源点灯制御回路23は、平版刷版10の搬送方向先端を検知したときに、ON操作の制御信号をLED光源用電源25へ送信して、LED20Aを点灯する。なお、このLED20Aを点灯させる制御では、平版刷版10の搬送方向先端を検知したときに直ちにLED20Aを点灯させる。または、この光源点灯制御回路23は、平版刷版10の搬送方向先端が露光補助部材16の直前に至るまでの点灯用所定待機時間をタイマで計り、平版刷版10の搬送方向先端を検知してから、点灯用所定待機時間を経過した時点でLED20Aを点灯させても良い。

[0087] また、この光源点灯制御回路23は、平版刷版10の搬送方向後端を検知したときに、平版刷版10の搬送方向後端が露光補助部材16を通過し終えるまでの消灯用所定待機時間をタイマで計り、この消灯用所定待機時間が経過した時点でLED20Aを消灯させるように制御する。

[0088] このように点灯制御ユニットによって、平版刷版10に対して後露光処理を行うときだけLED20Aを点灯するように制御する。これにより、後露光処理をしていないときにLED20Aを点灯するようなエネルギーの無駄を省き、後露光装置でLED20Aを使用できる期間(後露光装置で使用されているときのLED20Aの使用寿命)を長くすることができる。すなわち、この後露光装置では、LED20Aを点灯し続けて使用するときよりも、こまめに点灯と消灯を行った場合のほうがLED20Aを点灯させている時間を短くできるので、後露光装置でLED20Aを使用できる期間を長くできる。

[0089] また、光照射ユニット20としてLED20Aを用いる場合には、LED20Aが余分な赤外線を発生させることが無く、長寿命で均一な照明が可能となる。

[0090] 次に、上述のように構成した本第1実施の形態に係わる平版刷版用の後露光装置における、平版刷版の後露光動作について説明する。

[0091] この平版刷版用の後露光装置では、現像処理後の平版刷版10を図示しない供給ユニットによって後露光装置へ搬入する。

[0092] そして、後露光装置へ搬入された現像処理後の平版刷版10は、搬送路上流側に配置された一対の搬送ローラ12、14の間へ搬入されて搬送される。これにより、液体

シャワーバー26の下でノズルから噴射された液体が平版刷版10の表面上に供給されて平版刷版10の表面に液体の薄い膜を形成する。

[0093] この平版刷版10は、さらに搬送されて、露光補助部材16の下の後露光位置に至る。このとき、点灯制御ユニットによって、光照射ユニット20であるLED20Aが点灯される。さらに、平版刷版10上にある液体の層が、露光補助部材16に押し延べられて、平版刷版10と露光補助部材16との間は、隙間空間内に液体が充満し、かつ空気の泡等が存在しない状態とされる。

[0094] この後露光装置では、平版刷版10を搬送しながら、点灯された千鳥格子状に配置された複数のLED20Aで構成されたLEDアレイ光源から、平版刷版10の幅方向全幅に渡りかつ搬送方向に所定の長さを持つ所定範囲をいわゆる面露光状態で露光する。これにより、平版刷版10の全面を平均的に後露光する。

[0095] この後露光装置では、露光補助部材16のある後露光位置から搬送方向下流側の搬送ローラ12、14の位置まで平版刷版10が搬送される間、平版刷版10の画像記録層が液体に被われた状態となり空気中の酸素から遮断された状態を維持する。これにより、画像記録層において、酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進めて、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の耐刷性を向上することができる。

[0096] この後露光装置では、光源点灯制御回路23の制御により、版端検出センサ21が平版刷版10の搬送方向後端を検知したときからタイマで計測して消灯用所定待機時間を経過した時点でLED20Aを消灯させる。

[0097] 前述のように平版刷版10は、露光補助部材16がある後露光位置で後露光処理された後、搬送ローラ12、14で表面の液体が絞り落とされ、その搬送方向下流側にある乾燥器39から吹き付けられる温風により乾燥されて、搬出される。

[0098] この後露光装置では、大気中を搬送する搬送路上を搬送されている平版刷版10に対して、後露光位置前後の所定範囲内でのみ平版刷版10の現像済みの画像記録層上に薄い液体の膜である液膜を形成し酸素を遮断した状態で後露光を行う。このため、後露光処理時に酸素を遮断するために用いる液体の量を、必要最小限の少ない量にできる。

- [0099] この後露光装置では、後露光処理時に酸素を遮断するために用いる少量の液体を、液体循環系のフィルタ34とポンプ36とを用いて液に紛れ込むゴミを除去しながら循環して使用する。これにより、非常に少ない液体量で平版刷版10の後露光処理に必要な部分を確実に酸素遮断して良好に後露光処理することができる。
- [0100] この後露光装置では、液体循環系のフィルタ34を通すことによりゴミを除去した液体を平版刷版10の画像記録層に供給する。これにより、液中に浮遊するゴミにより後露光されない部分が発生することを防止できる。
- [0101] この後露光装置では、大気中を搬送する搬送路上を、画像記録層を上に向けて搬送されている平版刷版10に対して後露光用の光を上方から照射して後露光処理できる。これにより、LEDアレイ光源を、平版刷版10上の液体及び液体を流下させる液体シャワーバー26よりも高い位置に配置することができ、液跳ねが有ったり又は万一液漏れが有った場合でも、LEDアレイ光源が液体で濡れることを防止できる。
- [0102] 次に、本発明の平版刷版用の露光用器具を備えた後露光装置に係わる第2実施の形態について図3乃至図5により説明する。本第2実施の形態に係わる平版刷版用の後露光装置では、露光補助部材16に、液体を平版刷版10上に供給するユニットを一体的に構成する。
- [0103] この図3に示す第2実施の形態に係わる後露光装置では、平版刷版10を大気中で搬送する搬送路上の後露光位置の前後に、それぞれ一対のニップローラである搬送ローラ12、14を配置し、搬送路の露光位置上に所定距離だけ離間して、後露光に用いる器具である液体供給ユニットを備えた露光補助部材16を配置する。
- [0104] この後露光用器具としての液体供給ユニットを備えた露光補助部材16は、透明のガラス又はプラスチック等の材料で構成される。例えば図4及び図5に示すように、露光補助部材16は、矩形状の部材本体16A、長手方向の端面側部材16B、短手方向の一方の端面部材16C、及び管部材32に接続させるための接続端部材16Dを有する。
- [0105] この部材本体16Aには、その搬送方向上流側に当たる長手方向の端面部に、U字状の導液溝17Aを形成する。さらに部材本体16Aには、導液溝17Aの平版刷版10側に隣接させる側に当たる端部17Bの突出量が、導液溝17Aの平版刷版10から離

間した側に当たる端部17Cの突出量よりも液体供給用開口の幅だけ短くなるように形成する。

[0106] 端部17Cには、部材本体16Aの長手方向と同じ長さで部材本体16Aの厚さと同じ幅の直方体に形成した端面側部材16Bを、気密を保つように固着する。

[0107] この部材本体16Aに端面側部材16Bを固着し、それらの長手方向の一方の端部には、端面部材16Cを、他方の端部には、接続端部材16Dを、気密を保つように固着する。

[0108] この接続端部材16Dには、管部材32の管口部分が固着されている。この接続端部材16Dは、部材本体16Aに固着された状態で、接続端部材16Dに一端部を固着された管部材32の管口を、導液溝17Aと連通させるように構成する。

[0109] 露光補助部材16では、管部材32の管口に連通する導液溝17Aと、部材本体16Aの端部17Bと端面側部材16Bとの間に形成された液体供給用開口とが、断面鉤形に連通した液体供給路を形成する。

[0110] 露光補助部材16は、管部材32から送給された液体(ここでは水)を液体供給路の導液溝17Aから液体供給用開口を通じて、平版刷版10上へ適量ずつ流下させる機能を持つ。

[0111] 図3に示すように、後露光装置は、露光補助部材16の直下に当たる搬送路の下側にガイドローラ40を配置して、平版刷版10の下側面をガイドするように構成する。

[0112] 後露光装置は、後露光処理を行う際に、搬送ローラ12、14とガイドローラ40とによって搬送されている平版刷版10の画像記録層上に対し、露光補助部材16の搬送方向上流側にある液体供給用開口から、平版刷版10の幅方向全長に渡って略均等に適量の液体を流下させる。

[0113] すると、露光補助部材16の液体供給用開口から流下した液体は、平版刷版10の搬送動作と相俟って、平版刷版10の画像記録層と露光補助部材16の下面全体との間に充填され、空気の泡が混入しないように満たされる。露光補助部材16は、露光補助部材16における搬送方向上流側にある液体供給用開口から液体を流下する。これにより、液体が直ちに平版刷版10と露光補助部材16の下面全体との間に広がって迅速に充滿する。このため、比較的少ない量の液体で効率良く平版刷版10と露

光補助部材16との間に液体を充満させることができ、しかも平版刷版10と露光補助部材16との間に充満されてできた液体の層の厚さを比較的容易に厚くすることができる。

[0114] なお、このとき、平版刷版10上に供給された液体は、後露光位置より搬送方向上流側の搬送ローラ12、14と、後露光位置より搬送方向下流側の搬送ローラ12、14との間に広がって、表面張力により層状に溜まる状態となる。

[0115] この平版刷版用の後露光装置では、露光補助部材16と平版刷版10との間に液体を満たした状態で、搬送ローラ12、14によって平版刷版10を搬送しながら、光照射ユニット20から出射された後露光用の光を、後露光位置の所定範囲でいわゆる面露光して後露光処理をする。

[0116] このとき、現像処理済みの平版刷版10の画像記録層は、液体に被われて空気中の酸素から遮断された状態が維持される。これにより、現像処理済みの画像記録層において、酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進めて、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の耐刷性を向上することができる。

[0117] なお、本第2実施の形態の後露光装置における以上説明した以外の構成、作用、及び効果は前述した第1実施の形態と同様であるので、その説明を省略する。

[0118] 次に、本発明の平版刷版用の後露光装置に係わる第3実施の形態について図6により説明する。この第3実施の形態に係わる後露光装置では、搬送路上の後露光位置よりも搬送方向上流側に直近の搬送ローラ12を利用して、液体を平版刷版10上に供給するよう構成する。また、この第3実施の形態に係わる後露光装置では、平版刷版10上に液体の層を形成した状態で、露光補助部材を介することなく直接的に光照射ユニット20で後露光処理を行うよう構成する。

[0119] このため、後露光位置よりも搬送方向上流側に直近の搬送ローラ12における搬送ローラ12の中心を通る鉛直線よりも搬送方向下流側の外周面上に液体シャワーバー26から液体を流下させるように構成する。

[0120] また、この後露光装置では、後露光位置よりも搬送方向上流側に直近の搬送ローラ12の外周面に沿って液体を平均的に流すようにガイドする流下ガイド部材15を設

置する。

- [0121] この流下ガイド部材15は、円弧状のガイド部分15Aと、導入ガイド部15Bと、排出ガイド部15Cとを有する。円弧状のガイド部分15Aは、搬送ローラ12の外周面に対して所定間隔を開けて配置される。導入ガイド部15Bは、円弧状のガイド部分15Aの上端部から搬送ローラ12の略ラジアル方向に向けて延出する。排出ガイド部15Cは、円弧状のガイド部分15Aの下端部から平版刷版10の表面に対して所定間隔を開けて平行に延出する。
- [0122] また、この搬送ローラ12の部分には、導入ガイド部15Bと所定間隔を開けて対向する状態で搬送ローラ12の接線方向に延出するように補助流下ガイド部材19を配置する。補助流下ガイド部材19は、流下ガイド部材15の導入ガイド部15Bと協働して液体シャワーバー26から流下する液体を溢さないように受ける。
- [0123] このように構成した本第3実施の形態に係わる後露光装置では、液体シャワーバー26から流下した液体を導入ガイド部15Bと補助流下ガイド部材19とで受けて、搬送ローラ12の外周面と円弧状のガイド部分15Aとの間に導入し、これらの間を搬送ローラ12の外周面に沿うように流して、平版刷版10上へ導く。このように平版刷版10上に導かれた液体は、排出ガイド部15Cにガイドされて平版刷版10の画像記録層全面上に平均的に供給され、後露光位置より搬送方向上流側と搬送方向下流側とにそれぞれ配置された搬送ローラ12、14との間に広がって、表面張力により所定厚さの層状に溜まる状態となる。
- [0124] このように構成した場合には、後露光位置より搬送方向上流側の直近に配置された搬送ローラ12と、後露光位置より搬送方向下流側の直近に配置された搬送ローラ12との間に、液体シャワーバー26から液体を流下させるためのスペースを設けずに済む。これにより、後露光位置より搬送方向上流側の直近に配置された搬送ローラ12と、後露光位置より搬送方向下流側の直近に配置された搬送ローラ12との間を接近させて配置することができ、後露光装置を小型化することができる。
- [0125] また、この後露光装置では、後露光位置の上方に光照射ユニット20としての複数のLED20Aを設けたLEDアレイ光源を配置する。LED20Aから液体の薄い酸素遮断用の層を介して平版刷版10の現像処理済みの画像記録層に、後露光用の光を照

射する。

- [0126] 後露光装置では、平版刷版10の現像処理済みの画像記録層に形成される酸素遮断用の液体の層の表面に多少の凹凸が発生しても、LED20Aから光を照射して後露光処理を行う上で支障がない。これは、記録用のレーザービームを平版刷版10の画像記録層に合焦させる場合と異なり、平版刷版10の現像処理済みの画像記録層に後露光用の所定波長の光を照射してラジカル重合反応を生じさせることができれば良いので、酸素遮断用液体層の表面にできた凹凸で後露光用の光が散乱しても、ラジカル重合反応を生じさせることに影響が無いためである。
- [0127] なお、前述した図1及び図2に示す第1実施の形態でも、露光補助部材16を省略してLED20Aから酸素遮断用の液体の層を介して平版刷版10の現像処理済みの画像記録層に後露光用の光を照射するように構成しても良い。
- [0128] また、この後露光装置では、液体シャワーバー26から液体が流下される搬送ローラ12に対応して流下ガイド部材15を設ける。これにより、流下した液体が跳ね返って光照射ユニット20としてのLED20Aに付着することを防止できる。
- [0129] なお、本第3実施の形態の後露光装置における以上説明した以外の構成、作用、及び効果は前述した第1実施の形態と同様であるので、その説明を省略する。
- [0130] 次に、本発明の第4－6実施の形態の露光装置及び露光用器具について、図7－11により説明する。尚、上記第1－3実施の形態と同様の構成については説明を省略する。
- [0131] 本発明の第4実施の形態の露光装置及び露光用器具について、図7、8により説明する。図7、図8に示す露光装置では、露光補助部材16を介して露光処理するために、光ビーム照射ユニットである照射ヘッド320を設ける。この照射ヘッド320は、デジタル画像情報に基づいて変調された赤外線、可視光線又は紫外線等の所定の波長を有するレーザービームを出射するように構成する。この露光装置では、照射ヘッド320から出射された記録用のレーザービームを、高速回転されるポリゴンミラー322で反射し、さらに反射板324で反射し、露光位置で副走査方向に移動走査するように構成する。
- [0132] なお、この露光装置では、光ビーム照射ユニットとして、空間光変調素子を利用し

て面露光するユニット、又はLEDアレイ若しくは光ファイバとLDとを組み合わせた光源を複数配列してなるLDアレイ光源などを用いて、複数の記録を同時に行う、いわゆるマルチビーム露光を利用するユニット等を利用することができる。

- [0133] また、図7に想像線で示すように、露光補助部材16の直下に当たる搬送される平版刷版10の下側(裏側)には、ガイド部材318を設置しても良い。ガイド部材318は、平版刷版10の裏面に摺接して支持することにより、平版刷版10の表面と露光補助部材16との間の間隔を所定距離に保つ。ガイド部材318を配置した場合には、搬送されている平版刷版10の振動を抑え、平版刷版10の画像記録層に常に適切に合焦した状態で露光処理することができる。また、このガイド部材318は、平版刷版10の下面に摺接してガイドするもの又は転接してガイドするローラ等で構成しても良い。
- [0134] 次に、上述のように構成した本第4実施の形態に係わる平版刷版用の露光装置における、平版刷版の露光動作について説明する。
- [0135] この平版刷版用の露光装置では、図示しない平版刷版の原版を供給手段によって露光装置へ接続した搬送路上へ供給する。
- [0136] そして、搬送路上を搬送された平版刷版10は、搬送路上流側に配置された一对の搬送ローラ12、14の間へ搬入されて搬送される。液体シャワーバー26のノズルから噴射された液体が平版刷版10の表面上に供給されて平版刷版10の表面に液体の薄い膜を形成する。
- [0137] この平版刷版10は、さらに搬送されて、露光補助部材16の下で露光位置に至る。このとき、平版刷版10上にある液体の層は、露光補助部材16に押し延べられる。平版刷版10と露光補助部材16との間の隙間空間内に液体が充満し、かつ空気の泡等が存在しない状態とされる。
- [0138] この露光装置では、平版刷版10を、露光補助部材16がある露光位置を先端から後端にかけて主走査方向に移動走査しながら、照射ヘッド320からデジタル画像情報に基づいて変調されて出射された記録用のレーザービームを、高速回転されるポリゴンミラー322で反射し、さらに反射板324で反射することによって、露光位置で副走査方向に移動走査する。このように露光補助部材16は、平版刷版10の画像記録層に結像して露光し2次元画像(潜像)を記録する。

- [0139] この露光装置では、露光補助部材16のある露光位置から搬送方向下流側の搬送ローラ12、14の位置まで平版刷版10が搬送される間、平版刷版10の画像記録層が液体に被われた状態となり空気中の酸素から遮断された状態を維持する。これにより、画像記録層において、酸素による重合阻害が発生することなく効率よくラジカル重合反応を進め、良好にポリマー化して潜像を形成できる。
- [0140] このように露光補助部材16の露光位置で露光処理された平版刷版10は、搬送ローラ12、14で表面の液体が絞り落とされ、その搬送方向下流側にある乾燥器39から吹き付けられる温風により乾燥されて、次の処理工程へ搬出される。
- [0141] このように潜像が形成された平版刷版10は、この後、現像処理されて画像が形成された平版刷版10として完成される。このようにして画像が形成された平版刷版10は、図示しない印刷機に装着して印刷の用に供される。
- [0142] この露光装置では、大気中を搬送する搬送路上を搬送されている平版刷版10に対して、露光位置前後の所定範囲内でのみ平版刷版10の画像記録層上に薄い液体の膜である液膜を形成し酸素を遮断した状態で走査露光を行う。これにより、露光処理時に酸素を遮断するために用いる液体の量を、必要最小限の少ない量にできる。
- [0143] この露光装置では、大気中を搬送する搬送路上を、画像記録層を上に向けて搬送されている平版刷版10に対して、記録用のレーザービームを露光位置で上方向から照射して露光処理できる。露光ユニットを構成する照射ヘッド320、ポリゴンミラー22及び反射板324等を、平版刷版10上の液体及び液体を流下させる液体シャワーバー26よりも高い位置に配置する。これにより、液跳ねがあつたり又は万一液漏れがあつた場合でも、露光ユニットを液体で汚すことを防止できる。
- [0144] 次に、本発明の平版刷版用の露光装置及び露光用器具に係わる第5実施の形態について主に図9により説明する。本第2実施の形態に係わる平版刷版用の露光装置では、露光補助部材16に対して液体を平版刷版10上に供給する手段を一体的に構成する。
- [0145] この図9に示す第5実施の形態に係わる露光装置では、平版刷版10を大気中で搬送する搬送路上の露光位置の前後に、それぞれ一対のニップローラである搬送ロー

ラ12、14を配置し、搬送路の露光位置上に所定距離だけ離間して、露光用器具である液体供給手段を備えた露光補助部材16を配置する。この露光補助部材16の構成は、第2実施の形態と同様である(図4、及び図5参照)。

[0146] この露光用器具である露光補助部材16は、管部材32から送給された液体(ここでは水)を液体供給路の導液溝17Aから液体供給用開口を通じて、平版刷版10上へ適量づつ流下させる。

[0147] 平版刷版10上に供給された液体は、露光位置より搬送方向上流側の搬送ローラ12、14と、露光位置より搬送方向下流側の搬送ローラ12、14との間に広がって、表面張力により層状に溜まる状態となる。

[0148] この平版刷版用の露光装置では、露光補助部材16と平版刷版10との間に液体を満たした状態で、搬送ローラ12、14によって主走査方向に移動走査しながら、照射ヘッドからデジタル画像情報に基づいて変調されて出射された記録用のレーザービームを、高速回転されるポリゴンミラーで反射し、さらに反射板324で反射することによって、露光位置で副走査方向に移動走査する。このように平版刷版10の画像記録層に結像して露光し2次元画像(潜像)を記録する。

[0149] このとき、平版刷版10の画像記録層は、液体に被われて空気中の酸素から遮断された状態が維持される。これにより、画像記録層において、酸素による重合阻害が発生することなく効率よくラジカル重合反応を進め、良好にポリマー化して潜像を形成できる。

[0150] なお、本第5実施の形態における以上説明した以外の構成、作用、及び効果は前述した第4実施の形態と同様であるので、その説明を省略する。

[0151] 次に、本発明の平版刷版用の露光装置に係わる第6実施の形態について図10及び図11により説明する。この第6実施の形態に係わる露光装置では、搬送路上の露光位置よりも搬送方向上流側に直近の搬送ローラ12を利用して、液体を平版刷版10上に供給するよう構成する。

[0152] このように構成した本第6実施の形態に係わる露光装置では、液体シャワーバー26から流下した液体を導入ガイド部15Bと補助流下ガイド部材19とで受けて、搬送ローラ12の外周面と円弧状のガイド部分15Aとの間に導入して、これらの間を搬送ローラ

12の外周面に沿うように流して、平版刷版10上へ導く。このように平版刷版10上に導かれた液体は、排出ガイド部15Cにガイドされて平版刷版10の画像記録層上に平均的に供給されて所定厚さの層状に溜められた状態となり露光補助部材16の下面との間に充填され、露光位置より搬送方向上流側と搬送方向下流側とにそれぞれ配置された搬送ローラ12、14との間に広がって、表面張力により層状に溜まる状態となる。

[0153] このように構成した場合には、露光補助部材16と、これより搬送方向上流側の直近に配置された搬送ローラ12との間に、液体シャワーバー26から液体を流下させるためのスペースを設けずに済む。このため、露光補助部材16と搬送ローラ12、14とを接近させて配置することにより、露光装置を小型化することができる。また、この露光装置では、液体シャワーバー26から液体が流下される搬送ローラ12に対して、流下ガイド部材15を設ける。これにより、流下した液体が跳ね返って露光補助部材16の表面に付着することを防止できる。

[0154] なお、本第6実施の形態における以上説明した以外の構成、作用、及び効果は前述した第4実施の形態と同様であるので、その説明を省略する。

[0155] 次に、本発明の第7実施の形態に係わる平版刷版の現像方法及び装置について、図12乃至図17により説明する。尚、本発明の第1－3実施の形態と同様の構成については説明を省略する。本実施の形態に係わる平版刷版の現像装置は、図16に示す前処理部200と、図17に示す現像処理部100とで構成する。

[0156] この前処理部200は、いわゆるフォトポリマー版である平版刷版10に対し、現像処理に先立って前加熱処理及び前水洗処理を施すように構成する。この前処理装置200によって前処理された平版刷版10は、現像処理部100によって現像処理される。また、本実施の形態に適用した前処理部200は、現像処理部100と別に単独で 사용되는ものであってもよく、この現像処理部100に連結して使用してもよい。

[0157] この自動現像装置で現像される平版刷版10は、例えば、一般に用いられるいわゆるフォトポリマー版(感光性平版印刷版)である。アルミニウム等を用いた薄板の支持体の一方の面に、接着層を介して画像記録層(感光層)を形成し、その上にオーバーコート層を設けている。なお、この平版刷版10に対しては、一般に用いられる種々

の露光ユニットで画像を露光して潜像を形成する。

- [0158] この前処理装置200には、機枠202内に、前加熱部204を平版刷版10の搬送方向上流側に設け、前水洗工程としての前水洗部206を下流側に設ける。
- [0159] 前加熱部204には、加熱室208内に複数本の串型ローラ210を配置する。また、加熱室208内には、入口212側にヒータ214が設けられ、ヒータ214に通風するための循環ファン216が設けられている。
- [0160] 前加熱部204では、平版刷版10が加熱室208内を通過するときに、所定の温度及び所定の加熱時間となるようする。これにより、平版刷版10の光重合層を的確に硬化させて、平版刷版10の耐刷力の増加を図っている。
- [0161] 一方、加熱室208内を通過した平版刷版10は、出口218から前水洗部206へ送られる。
- [0162] 前水洗部206には、水洗タンク220が設けられている。この水洗タンク220内に洗浄水を貯留する洗浄槽222が形成されている。
- [0163] 前水洗部206には、前加熱部204側に、搬送ローラ224、226、228が千鳥状に配置されている。搬送ローラ224、228は、平版刷版10の上面に対向するように設けられる。搬送ローラ226は、搬送ローラ224、228の間で、平版刷版10の下面に対向するように配置されている。
- [0164] これらにより、前水洗部206へ送り込まれた平版刷版10は、搬送ローラ224、228と搬送ローラ226との間に挟まれる状態で搬送される。
- [0165] 前水洗部206には、搬送ローラ228の下流側に、ブラシローラ230とバックアップローラ232が、上下に対で設けられている。ブラシローラ230とバックアップローラ232の接触位置は、搬送ローラ228の下端よりも低くなっている。これにより、平版刷版10は、搬送ローラ226、228の間から傾斜されてブラシローラ230とバックアップローラ232の間へ送り込まれる。
- [0166] また、前水洗部206には、搬送ローラ228とブラシローラ230の間にスプレーパイプ234が設けられ、ブラシローラ230の上方にスプレーパイプ236が設けられている。
- [0167] スプレーパイプ236は、ブラシローラ230の軸線方向に沿った全域に渡って洗浄水を噴射してブラシ素材に洗浄水を供給する。従って、平版刷版10は、洗浄水が供給

されたブラシローラ230によってブラッシングされる。

- [0168] また、平版刷版10には、スプレーパイプ234から表面に洗浄水が供給される。さらに、平版刷版10は、その表面に洗浄水が溜められた状態で、ブラシローラ230とバックアップローラ232との間へ送り込まれる。
- [0169] この平版刷版10では、表面に洗浄水が溜まった状態となると、平版刷版10に設けているオーバーコート層が洗浄水によって膨潤して剥がれ易い状態となる。このため、ブラシローラ230によってブラッシングすることにより、オーバーコート層を確実に除去することができる。部分的にオーバーコート層が残って現像処理を行ったときに、現像ムラを生じさせてしまうことを防止することができる。
- [0170] この平版刷版10は、所定方向に回転された状態のブラシローラ230とバックアップローラ232との間を通過する際に、ブラシローラ230によって平版刷版10の表面がブラッシングされる。なお、ブラシローラ230は、バックアップローラ232との間で平版刷版10を挟んだときに、所定のブラシ圧が得られるように装着されている。
- [0171] 一方、前水洗部206には、ブラシローラ230の下流側に、串型ローラ238が設けられている。この串型ローラ238は、平版刷版10の搬送路の上方側に配置されており、ブラシローラ230とバックアップローラ232の間を通過した平版刷版10が、ブラシローラ230によってブラッシングされることにより浮き上がって、搬送路から外れてしまうのを防止する。
- [0172] また、前処理部200を現像処理部100と連結する場合には、前水洗部206の最下流に、現像処理部100の搬送ローラ対142を設けるものとする。
- [0173] 図17に示す自動現像装置は、露光装置(図示せず)によって画像が露光された平版刷版10を現像処理するのに用いる。
- [0174] この現像処理部100は、平版刷版10を現像液によって処理するための現像部114と、水洗部117と、不感脂化处理部118と、平版刷版10を乾燥させる乾燥部120とを有する。水洗部117は、現像液によって処理された平版刷版10の水洗水を供給して水洗すると共に後露光処理をする後露光処理部を兼ねている。
- [0175] すなわち、現像処理部100では、平版刷版10の搬送方向(図の矢印A方向)に沿って、現像工程、水洗及び後露光処理工程、不感脂化处理工程及び乾燥工程を順

に配置する。

- [0176] 現像処理部100内には、処理タンク122が設けられている。この処理タンク122には、処理槽として現像部114となる位置に現像槽124、後露光処理部を兼ねた水洗部117となる位置に受け皿部材428、及び不感脂化处理部118となる位置に不感脂化处理槽128が形成されている。また、処理タンク122には、現像槽124の上流側（平版刷版10の搬送方向の上流側）に挿入部134のスペースが設けられ、不感脂化处理槽128の下流側に乾燥部120のスペースが形成されている。
- [0177] 処理タンク122の周囲を覆う外板パネル130には、現像処理部100への平版刷版10の挿入側（図17に向かって紙面左側）にスリット状の挿入口132が形成され、現像部114の挿入口132側に挿入部134が形成されている。
- [0178] 現像処理部100には、処理タンク122の上部及び乾燥部120の上部を覆うカバー136、138が設けられている。挿入口132側のカバー136は、処理タンク122の挿入部134から後露光処理部を兼ねた水洗部117の上部を覆う。カバー138は、後露光処理部を兼ねた水洗部117の上部から乾燥部120の上部の間を覆うように配置される。
- [0179] また、カバー136には、現像部114と後露光処理部を兼ねた水洗部117との間に平版刷版10を挿入するためのリエントリー用の挿入口（副挿入口）140が設けられている。この副挿入口140には、現像部114での処理を除く自動現像装置（PS版プロセッサ）100での処理を行うための平版刷版10を挿入する。
- [0180] 副挿入口140に隣接する挿入部134には、ゴム製の搬送ローラ対142が配設されている。画像が焼付けられた平版刷版10は、挿入口132から矢印A方向に沿って挿入されることにより、搬送ローラ対142の間に送り込まれる。
- [0181] 搬送ローラ対142は、回転駆動されることにより、この平版刷版10を挿入口132から引き入れながら、水平方向に対して約15° から31° の範囲の角度で現像部114へ送り込む。なお、片面タイプの平版刷版10の処理に用いる現像処理部100では、画像記録層（感光面）が上方へ向けられた状態で挿入口132から挿入される。すなわち、平版刷版10は、感光面を上方へ向けられた状態で現像処理部100によって処理される。

- [0182] 処理タンク122に形成されている現像槽124は、底部中央が下方へ向けて突出された略山形状となっており、平版刷版10の現像処理を行うためのアルカリ現像液を貯留する。
- [0183] この現像槽124内には、平版刷版10の搬送路の上流部となる挿入部134側に搬送ローラ148が配置されている。また、現像槽124内には、PS版の搬送路の中央部に搬送ローラ対150が配置され、下流部となる後露光処理部を兼ねた水洗部117側に搬送ローラ対152が配置されている。
- [0184] 現像処理部100の現像槽124には、搬送ローラ148と搬送ローラ対150の間にガイド116が設けられる。このガイド116は、一端部が搬送ローラ148に対向し、他端部が搬送ローラ対150の間へ向けられている。
- [0185] これにより、搬送ローラ対142によって現像処理部100内に引き入れられた平版刷版10は、搬送ローラ148とガイド116の間に送り込まれ、ガイド116上を搬送ローラ対150の間へ案内搬送される。
- [0186] また、現像槽124内には、搬送ローラ対150の近傍に、ガイド116に対向してブラシローラ141が配置される。ブラシローラ141は、所定回転方向及び所定の回転速度で回転駆動して、ガイド116上を搬送される平版刷版10の表面に接触することにより、平版刷版10の上面をブラッシングする。なお、ガイド116は、ブラシローラ141が所定のブラシ圧で平版刷版10の上面に接触するように装着されている。
- [0187] また、ブラシローラ141は、アルカリ現像液の液面から突出するようになっている。遮蔽蓋101の凹部101Bには、搬送ローラ対150と共に、ブラシローラ141の液面から突出した上部が入り込むようになっている。
- [0188] 一方、現像槽124内には、搬送ローラ対150、152の間に、ブラシローラ143と搬送ローラ160が配置されている。ブラシローラ143及び搬送ローラ160は、搬送ローラ対150、152の間を搬送される平版刷版10の上面側に対向するように取り付けられている。ブラシローラ143は、所定方向及び所定の回転方向に回転しながら平版刷版10の上面に接触することにより、平版刷版10の上面側の画像記録層をブラッシングして、現像液によって不要な画像記録層の除去を促進するようになっている。
- [0189] 搬送ローラ対142によって挿入口132から引き入れられた平版刷版10は、搬送ロ

ーラ148の下方を通過して、ブラシローラ141によってブラッシングされた後に、搬送ローラ対150の間へ送り込まれ、さらに、搬送ローラ150によって現像槽124内のガイド部材147に沿うように搬送ローラ対152へ向けて斜め上方へ案内される。このとき、平版刷版10の上面側がブラシローラ143によってブラッシングされる。

[0190] また、搬送ローラ対152は、例えば外周部がゴム製のローラによって形成されており、平版刷版10を挟持して現像槽124から引き出しながら、後露光処理部を兼ねた水洗部117へ送り込む。

[0191] 現像槽124内には、搬送ローラ対150と搬送ローラ対152の間のガイド部材147近傍にスプレーパイプ156が設けられている。このスプレーパイプ156には、図示しないポンプによって吸引した現像槽124内の現像液が供給される。このスプレーパイプ156から供給された現像液が噴出される。これにより、現像槽124内の現像液が攪拌されて、平版刷版10の均一な処理が可能となる。

[0192] 搬送ローラ対152によって現像槽124から搬出された平版刷版10は、この搬送ローラ対152によって表面に付着している現像液が絞り落とされながら、後露光処理部を兼ねた水洗部117へ送り込まれる。

[0193] 上述のように、平版刷版10の画像記録層に対して露光処理をしてラジカル光重合によってポリマー化させて潜像を形成する。この後、平版刷版に対してアルカリ現像液に浸漬した状態でブラシローラによって潜像が形成された画像記録層における未露光の部分除去して露光された画像記録層部分だけを残す。この後露光処理部を兼ねた水洗部117は、このように画像を顕在化した平版刷版に対して、アルカリ等の現像液を洗浄すると共に後露光処理を行った後に、不感脂化処理部118へ送り出す。

[0194] 平版刷版10が露光処理後に現像処理されることにより、画像記録層におけるポリマー化した部分だけがアルミニウム支持体上に残って画像が形成される。このとき、現像処理後の平版刷版10では、アルミニウム支持体上に画像を形成するように残っている画像記録層の部分が十分にポリマー化されているとは限らない。画像記録層の部分におけるアルミニウム支持体側の一部にポリマー化が不十分な所が残っている場合がある。

- [0195] そこで、後露光処理部を兼ねた水洗部117では、後露光処理によって、平版刷版10の全面に画像記録層の感光領域の波長を有する光で均等に露光する。これにより、アルミニウム支持体上に画像を形成するように残っている画像記録層の部分を全体に渡って十分にポリマー化することで硬化させ、耐刷性を向上させる。
- [0196] 図12及び図13に示す、平版刷版10の耐刷性向上用の後露光処理部を兼ねた水洗部117は、大気中を搬送する略水平の搬送路上を搬送されている画像が顕在化された平版刷版10に対して、水洗水を平版刷版10の表裏の各全面に噴出して現像液を洗い落とすと共に、平版刷版10の表面を水洗水が覆った酸素遮断状態で平版刷版10の耐刷性を向上する後露光処理を行う。このように、水洗部117は、平版刷版10の表面を水洗する構成と、平版刷版10の表面を水で覆って酸素遮断状態とする構成とを兼用している。これにより、部品点数を削減して構成を簡素化する。
- [0197] この後露光処理部を兼ねた水洗部117では、搬送路の上方に、液体供給ユニットとしての液体シャワーバー26を設置する。この液体シャワーバー26は、露光補助部材16とこれより搬送方向上流側に配置された搬送ローラ12、14との間の所定位置に、搬送方向に直交する方向に向けて、平版刷版10の幅方向全体に渡る範囲に対応して液体を噴射するように配置する。
- [0198] また、この後露光処理部を兼ねた水洗部117では、搬送路の下方に、洗浄用液体供給ユニットとしての液体シャワーバー427を設置する。この液体シャワーバー427は、露光補助部材16より搬送方向上流側に配置された搬送ローラ12、14と搬送方向下流側に配置された搬送ローラ12、14との間の所定位置に、搬送方向に直交する方向に向けて、平版刷版10の裏面の幅方向全体に渡る範囲に対応して液体を噴射するように配置する。
- [0199] この液体シャワーバー427は、例えば、前述した液体シャワーバー26と同様に構成され、その平版刷版10の裏面に向けた多数のノズル孔から液体(ここでは少なくとも現像液を洗浄する液体となる水)を各ノズルから噴射して平版刷版10の裏面から現像液を洗い流す。
- [0200] このように、液体シャワーバー427から噴射された液体は、平版刷版10の裏面に当たって現像液を洗い流し、受け皿部材428内へ流れ込む。

- [0201] また、この受け皿部材428と、液体シャワーバー26、427との間には、液体循環管路30を設置する。この一連の液体循環管路30を構成する管部材32と液体シャワーバー26、427との間には、フィルタ34、ポンプ36及びヒータ38を配置する。
- [0202] 次に、上述のように構成した図12及び図13に示す平版刷版用の後露光処理部を兼ねた水洗部117における、平版刷版の後露光動作について説明する。
- [0203] この平版刷版用の後露光処理部を兼ねた水洗部117では、現像処理後の平版刷版10を図示しない供給ユニットによって後露光処理部を兼ねた水洗部117へ搬入する。
- [0204] そして、後露光処理部を兼ねた水洗部117へ搬入された現像処理後の平版刷版10は、搬送路上流側に配置された一对の搬送ローラ12、14の間へ搬入されて搬送される。これにより、液体シャワーバー26の下でノズルから噴射された液体が平版刷版10の表面上に供給されて平版刷版10の表面に液体の薄い膜を形成する。
- [0205] このとき、平版刷版10は、液体シャワーバー26から噴射される水により画像記録層に付着している現像液が洗浄され、液体シャワーバー427から噴射される水により平版刷版10の裏面に付着している現像液が洗浄される。
- [0206] この平版刷版10は、さらに搬送されて、露光補助部材16の下の後露光位置に至る。このとき、点灯制御ユニットによって、光照射ユニット20であるLED20Aが点灯される。さらに、平版刷版10上にある液体の層は、露光補助部材16に押し延べられる。平版刷版10と露光補助部材16との間の隙間空間内に液体が充満し、かつ空気の泡等が存在しない状態とされる。
- [0207] この後露光処理部を兼ねた水洗部117では、平版刷版10を搬送しながら、点灯された千鳥格子状に配置された複数のLED20Aで構成したLEDアレイ光源が、平版刷版10の幅方向全幅に渡りかつ搬送方向に所定の長さを持つ所定範囲をいわゆる面露光状態で露光する。このように、平版刷版10の全面を平均的に後露光する。
- [0208] この後露光処理部を兼ねた水洗部117では、露光補助部材16のある後露光位置から搬送方向下流側の搬送ローラ12、14の位置まで平版刷版10が搬送される間、平版刷版10の画像記録層が液体に被われた状態となり空気中の酸素から遮断された状態を維持する。このため、画像記録層において、酸素による重合阻害の影響を

受けることなくラジカル重合反応を残らず進め、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の耐刷性を向上することができる。

- [0209] この後露光処理部を兼ねた水洗部117では、光源点灯制御回路23の制御により、版端検出センサ21が平版刷版10の搬送方向後端を検知したときからタイマで計測して消灯用所定待機時間を経過した時点でLED20Aを消灯させる。
- [0210] 前述のように露光補助部材16がある後露光位置で後露光処理された平版刷版10は、搬送ローラ12、14で表面の液体が絞り落とされ、その搬送方向下流側にある乾燥器39から吹き付けられる温風により乾燥されて、搬出される。
- [0211] この後露光処理部を兼ねた水洗部117では、現像液の洗浄に用いると共に後露光処理時に酸素を遮断するために用いる液体を、液体循環系のフィルタ34とポンプ36とを用いて液に紛れ込むゴミを除去しながら循環して使用する。
- [0212] この後露光処理部を兼ねた水洗部117では、液体循環系のフィルタ34を通すことによりゴミを除去した液体を平版刷版10の画像記録層に供給する。これにより、液中に浮遊するゴミにより後露光されない部分が発生することを防止できる。
- [0213] この後露光処理部を兼ねた水洗部117では、大気中を搬送する搬送路上を、画像記録層を上に向けて搬送されている平版刷版10に対して後露光用の光を上方から照射して後露光処理できる。LEDアレイ光源を、平版刷版10上の液体及び液体を流下させる液体シャワーバー26よりも高い位置に配置する。これにより、液跳ねが有ったり又は万一液漏れが有った場合でも、LEDアレイ光源が液体で濡れることを防止できる。
- [0214] 次に、この平版刷版の現像装置に用いる、平版刷版用の露光用器具を備えた後露光処理部を兼ねた水洗部117に係わる他の構成例について主に図14により説明する。この図14に示す平版刷版用の後露光処理部を兼ねた水洗部117では、露光補助部材16に対して液体を平版刷版10上に供給するユニットを一体的に構成する。この露光補助部材16の構成は、第2実施の形態と同様である(図4、及び図5参照)。
- [0215] この図14に示す後露光処理部を兼ねた水洗部117では、平版刷版10を大気中で搬送する搬送路上の後露光位置の前後に、それぞれ一対のニップローラである搬送ローラ12、14を配置し、搬送路の露光位置上に所定距離だけ離間して、後露光に

用いる器具である液体供給ユニットを備えた露光補助部材16を配置する。

[0216] この後露光に用いる器具である露光補助部材16は、管部材32から送給された液体(ここでは水)を液体供給路の導液溝17Aから液体供給用開口を通じて、平版刷版10上へ所要量ずつ流下させる。

[0217] この図14に示す後露光に用いる器具を備えた後露光処理部を兼ねた水洗部117では、後露光処理を行う際に、搬送ローラ12、14とガイドローラ40とによって搬送されている平版刷版10の画像記録層上に対し、露光補助部材16の搬送方向上流側にある液体供給用開口から、平版刷版10の幅方向全長に渡って略均等に所要量の液体を流下させる。

[0218] すると、露光補助部材16の液体供給用開口から流下した液体は、平版刷版10の搬送動作と相俟って、平版刷版10の画像記録層と露光補助部材16の下面全体との間に充填され、空気の泡が混入しないように満たされる。この後露光に用いる器具としての液体供給ユニットを備えた露光補助部材16では、露光補助部材16における搬送方向上流側にある液体供給用開口から液体を流下する。これにより、液体が直ちに平版刷版10と露光補助部材16の下面全体との間に広がって迅速に充填する。このため、比較的少ない量の液体で効率良く平版刷版10と露光補助部材16との間に液体を充填させることができる。しかも平版刷版10と露光補助部材16との間に充填されてできた液体の層の厚さを比較的容易に厚くすることができる。

[0219] このとき、平版刷版10上に供給された液体は、後露光位置より搬送方向上流側の搬送ローラ12、14と、後露光位置より搬送方向下流側の搬送ローラ12、14との間に広がるように流れて、平版刷版10の画像記録層に付着している現像液を洗い流す。

[0220] この後露光処理部を兼ねた水洗部117では、露光補助部材16と平版刷版10との間に液体を満たした状態で、搬送ローラ12、14によって平版刷版10を搬送しながら、光照射ユニット20から出射された後露光用の光を、後露光位置の所定範囲でいわゆる面露光して後露光処理をする。

[0221] このとき、現像処理済みの平版刷版10の画像記録層は、液体に被われて空気中の酸素から遮断された状態が維持される。これにより、現像処理済みの画像記録層において、酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進

め、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の耐刷性を向上することができる。

[0222] また、この後露光処理部を兼ねた水洗部117では、前述したように、液体シャワーバー427から噴射される液体によって、平版刷版10の裏面を洗浄する。

[0223] なお、上述した図14に示す平版刷版用の後露光処理部を兼ねた水洗部117における以上説明した以外の構成、作用及び効果は前述した図12及び図13に示す後露光処理部を兼ねた水洗部と同様であるので、その説明を省略する。

[0224] 次に、後露光処理部を兼ねた水洗部に係わるさらなる他の構成例について図15により説明する。この図15に示す後露光処理部を兼ねた水洗部117では、搬送路上の後露光位置よりも搬送方向上流側に直近の搬送ローラ12が、液体を平版刷版10の画像記録層上に供給する。また、この図15に示す後露光処理部を兼ねた水洗部117では、平版刷版10上に液体の層を形成するように洗浄している状態で、露光補助部材を介することなく直接的に光照射ユニット20で後露光処理を行う。

[0225] このため、後露光位置よりも搬送方向上流側に直近の搬送ローラ12における搬送ローラ12の中心を通る鉛直線よりも搬送方向下流側の外周面上に液体シャワーバー26から液体を流下させる。

[0226] また、この後露光処理部を兼ねた水洗部117では、前述したように、液体シャワーバー427から噴射される液体によって、平版刷版10の裏面を洗浄する。

[0227] なお、上述した図15に示す平版刷版用の後露光処理部を兼ねた水洗部117における以上説明した以外の構成、作用及び効果は前述した図12及び図13に示す後露光処理部を兼ねた水洗部と同様であるので、その説明を省略する。

[0228] 図17に示すように、この平版刷版の現像装置では、後露光処理部を兼ねた水洗部117で洗浄され後露光処理された平版刷版10を不感脂化处理部118へ搬出する。

[0229] 不感脂化处理部118には、不感脂化处理槽128の上方に搬送ローラ対170が設けられ、後露光処理部を兼ねた水洗部117から搬出された平版刷版10は、搬送ローラ対170によって不感脂化处理部118内を搬送された後に、乾燥部120へ向けて送られる。

[0230] 不感脂化处理部118には、平版刷版10の搬送路の上方側にスプレーパイプ172

が設けられ、搬送路の下方側にスプレーパイプ174が設けられている。スプレーパイプ172、174は、長手方向(軸線方向)が平版刷版10の幅方向に沿い、平版刷版10の搬送路を挟んで上下に配置されている。また、スプレーパイプ172、174には、平版刷版10の幅方向に沿って複数の吐出孔が形成されている。

[0231] 不感脂化处理槽128には、平版刷版10の版面保護に用いるガム液が貯留されている。このガム液は平版刷版10の搬送に同期してスプレーパイプ172、174に供給される。スプレーパイプ172は、このガム液を平版刷版10へ向けて滴下して平版刷版10の表面に広げて塗布する。また、スプレーパイプ174は、吐出孔から平版刷版10の裏面へ向けてガム液を吐出して、平版刷版10の裏面にガム液を塗布する。

[0232] 平版刷版10は、表裏面に塗布されるガム液によって保護膜が形成される。なお、スプレーパイプ172からのガム液の吐出方向は、平版刷版10の搬送方向下流側に限らず、他の方向であっても良い。また、整流板を設け、この整流板へ向けて噴出したガム液を、整流板で平版刷版10の幅方向に沿って均一に拡散させながら、平版刷版10の表面に流し落として塗布するようにしてもよい。また、スプレーパイプ174に換えて、吐出したガム液に平版刷版10が接触しながら移動することにより平版刷版10の裏面にガム液を塗布する吐出ユニット等を用いても良い。

[0233] なお、不感脂化处理部118には、搬送ローラ対170の上方に洗浄スプレー176が設けられ、搬送ローラ対170の上方のローラに接触しながら回転する洗浄ローラ178が設けられている。予め設定している所定のタイミングで、この洗浄スプレー176から搬送ローラ対170の上方のローラと洗浄ローラ178の接触位置に、整流板180を介して洗浄水を滴下する。これにより、洗浄水を搬送ローラ対170の上方のローラの周面に均一に拡散させて、搬送ローラ対170の上下のローラの周面からガム液を洗い流す。ローラの周面にガム液が固着して平版刷版10を損傷させてしまうことを防止するようにしている。

[0234] 不感脂化处理部118でガム液が塗布された平版刷版10は、搬送ローラ対170に挟持されて、表裏面にガム液が若干残った状態(ガム液が薄膜として残った状態)で乾燥部120へ送られる。

[0235] 現像処理部100には、不感脂化处理部118と乾燥部120の間に、仕切り板182が

設けられている。この仕切り板182は、平版刷版10の搬送路の上方に、処理タンク122の上端と対向するように配置されており、これにより、不感脂化处理部118と乾燥部120の間にスリット状の挿通口184が形成されている。なお、仕切り板182は、二重構造となっている。これにより、挿通口184の乾燥部120側に溝状の通気路が形成される。乾燥部120内の空気がこの通気路内に入り込むことにより、乾燥部120内の空気が挿通口184から不感脂化处理部118内に入り込んでしまうのを防止している。

[0236] 乾燥部120内には、挿通口184の近傍に、平版刷版10を支持する支持ローラ186が配設され、平版刷版10の搬送方向の中央部及び、排出口188の近傍には、搬送ローラ対190及び搬送ローラ対192が配設されている。平版刷版10は、支持ローラ186及び搬送ローラ対190、192によって乾燥部120内を搬送される。

[0237] 支持ローラ186と搬送ローラ対190との間、及び搬送ローラ対190と搬送ローラ対192との間には、平版刷版10の搬送路を挟んで対でダクト194、196が配設されている。ダクト194、196は、長手方向が平版刷版10の幅方向に沿って配設されており、平版刷版10の搬送路に対向する面にスリット孔198が設けられている。

[0238] ダクト194、196は、図示しない乾燥風発生ユニットによって発生された乾燥風が、長手方向の一端側から供給されると、この乾燥風をスリット孔198から平版刷版10の搬送路へ向けて吐出し、平版刷版10に吹き付ける。これにより、平版刷版10は、表裏面に塗布されているガム液が乾燥され、保護膜が形成される。

[0239] 現像処理部100では、現像槽124内に液面蓋101を配置する。これにより、現像槽124内の現像液が空気中の炭酸ガス等と接触してしまうことによる劣化や水分の蒸発を防止するようにしている。なお、遮蔽蓋101及び処理タンク122と搬送ローラ148や搬送ローラ対152等の間にシリコンゴム等によって形成したブレード状の遮蔽部材(図示省略)を設ける。これにより、現像槽124内の現像液が新鮮な外気と接触すること及び現像液中の水分が蒸発することを防止する。

[0240] 次に、上述のように構成した本第7実施の形態に係わる平版刷版の現像装置の作用及び動作について説明する。

[0241] この平版刷版の現像装置の前処理装置200は、画像を露光された平版刷版10が

、前加熱部204へ挿入されると、平版刷版10の搬送処理を開始する。これと共に、前処理装置200では、前水洗部206に設けたスプレーパイプ234、236へ洗浄槽22内の洗浄水を供給する動作を開始する。

[0242] 次に挿入口から挿入された平版刷版10が、機枠内に引き入れられると共に、加熱室208内へ送り込まれる。前加熱部204では、加熱室208内に送り込まれた平版刷版10をヒータ214によって加熱しながら搬送する。これにより、平版刷版10は、予め設定されている加熱温度及び加熱時間で加熱され、画像部の光重合層の重合度を増加させて耐刷力が増加されて、前水洗部206へ送り出される。

[0243] 前水洗部206では、千鳥状に配置している搬送ローラ224～228によって平版刷版10に搬送力を付与しながら、斜め下方へ向けて送り出す。これにより、平版刷版10は、ブラシローラ230とバックアップローラ232との間へ送り込まれる。

[0244] また、前水洗部206では、スプレーパイプ236から洗浄水を噴出する。この洗浄水をブラシローラ230へ供給すると共に、スプレーパイプ234から洗浄水を噴出する。

[0245] これにより、平版刷版10は、搬送ローラ226、228の間からブラシローラ230とバックアップローラ232の間へ搬送されるときに、ブラシローラ230とバックアップローラ232の間へ送り込まれてブラシローラ230によってブラッシングされる。

[0246] なお、平版刷版10は、表面に洗浄水が供給されることにより、最上層のオーバーコート層が膨潤して剥がれ易くなる。また、オーバーコート層は、洗浄水に漬かっている時間が長くなることにより、より剥がれやすくなっている。

[0247] このようにして、ブラッシングされてオーバーコート層が除去された平版刷版10は、現像処理部100の搬送ローラ対142に挟持されて、前処理部200から現像処理部100へと送り出される。

[0248] 現像処理部100では、図示しない画像露光装置によって露光処理されて潜像が形成された平版刷版10が、挿入口132から挿入されると、搬送ローラ対142を回転駆動させる。これにより、平版刷版10は、搬送ローラ対142によって挟持されて、自動現像装置内に引き入れられる。

[0249] なお、現像処理部100を含む自動現像装置では、挿入口132の近傍に、挿入口132を通過する平版刷版10を検出するセンサを設ける。このセンサが平版刷版10の

挿入を検出したときに搬送ローラ対142等の回転駆動を開始する。このセンサによる平版刷版10の検出に基づいたタイミングで、水洗部117のスプレーパイプ26、427からの水洗水の吐出及び不感脂化处理部118のスプレーパイプ172、174からのガム液の吐出を行うように制御する。なお、この自動現像装置では、センサによる平版刷版10の検出に基づいた所定のタイミングで、LED20Aを点灯又は消灯する制御を行うようにして、図13に示す版端検出センサ21を省略しても良い。

- [0250] 搬送ローラ対142は、挿入口132から引き入れた平版刷版10を、水平方向に対して 15° ～ 31° の範囲の挿入角度で、現像槽124へ送り込む。これにより、平版刷版10は、ガイド板116によって案内されながら搬送ローラ148及び搬送ローラ対150、152によって現像槽124内を搬送されて、現像槽124内に貯留されている現像液に浸漬され、 17° ～ 31° の範囲の排出角度で、現像液中から送り出される。
- [0251] 平版刷版10は、現像槽124内で現像液に浸漬されることにより、画像記録層の露光されなかった部分が支持体から除去される。このとき、自動現像装置では、現像槽124内に配置しているブラシローラ141、143によって平版刷版10の表面(画像記録層側の面)をブラッシングする。これにより、平版刷版10の表面からの不要な画像記録層の除去を促進するようにしている。
- [0252] 現像処理を終えて現像槽124から送り出される平版刷版10は、搬送ローラ対152によって後露光処理部を兼ねた水洗部117へ送られる。このとき、搬送ローラ対152は、平版刷版10の表裏面に付着している現像液を絞り落とす。
- [0253] 後露光処理部を兼ねた水洗部117では、この平版刷版10を搬送ローラ12、14によって挟持して略水平方向に搬送しながら、液体シャワーバー26、液体シャワーバー427から水洗水を噴出して、平版刷版10の表裏面に残っている現像液を洗い落とす。
- [0254] これと共に、後露光処理部を兼ねた水洗部117では、液体シャワーバー26から噴射した水で、画像記録層の表面を全体的に覆った状態で、LED20Aを点灯して後露光処理を行う。乾燥器39で乾燥してから、この平版刷版10を不感脂化处理部118へ送り出す。
- [0255] 不感脂化处理部118へ送られた平版刷版10は、スプレーパイプ172、174の間を

通過し、搬送ローラ対170に挟持され、この搬送ローラ対170によって不感脂化处理部118から送り出される。

[0256] このとき、不感脂化处理部118では、スプレーパイプ172、174からガム液を吐出して、平版刷版10の表裏面にガム液を拡散させながら均一に塗布する。搬送ローラ対170は、平版刷版10を挟持搬送して、余剰となったガム液を平版刷版10の表裏面から絞り落とす。これにより、平版刷版10の表裏面にガム液の均一な薄膜を形成する。

[0257] ガム液が塗布された平版刷版10は、搬送ローラ対170によって挿通口184から乾燥部120へ送り込まれる。なお、挿通口184にシャッタを設けているときには、平版刷版10の処理開始のタイミング又は平版刷版10が不感脂化处理部118から送り出されるタイミングで、シャッタを作動させて、挿通口184を開放する。これにより、平版刷版10の非通過時に乾燥部120の乾燥風が不必要に不感脂化处理部118へ入り込んで、搬送ローラ対170にガム液が固着してしまうのを防止している。挿通口184から空気が入り込み、現像部114にまで及んで空気中の炭酸ガスにより現像液が劣化するのを防止している。現像液中の水分や水洗水さらにガム液中の水分が蒸発して挿通口184から出てしまうのを防止している。

[0258] 乾燥部120では、支持ローラ186及び搬送ローラ対190、192によって平版刷版10を搬送しながら、ダクト194、196からこの平版刷版10の表裏面に乾燥風を吹き付ける。これにより、平版刷版10は、表面に塗布されているガム液による保護膜が形成される。排出口188から排出される。

[0259] 次に、本発明の第8の実施の形態に係る平版刷版の現像方法及び装置について、主に図18乃至図24により説明する。本実施の形態に係わる平版刷版の現像装置は、前処理部200(図16参照)と、図22に示す現像処理部100とで構成する。

[0260] この現像処理部100は、平版刷版10を現像液によって処理するための現像部114と、水洗部617と、保護層形成工程(不感脂化处理工程)とを有する。水洗部617は、現像液によって処理された平版刷版10へ水洗水を供給して水洗する。保護層形成工程は、平版刷版10の現像された表面に親水層保護の為にガム液を塗布してから乾燥する間に後露光処理をする後露光処理部を兼ねている。

- [0261] すなわち、現像処理部100では、平版刷版10の搬送方向(図の矢印A方向)に沿って、現像工程、水洗工程、保護層形成及び後露光処理工程を順に配置する。
- [0262] 現像処理部100内には、処理タンク122が設けられている。この処理タンク122には、処理槽として現像部114となる位置に現像槽124、水洗部617となる位置に受け皿部材628、保護層形成及び後露光処理部(不感脂化処理部及び後露光処理)618となる位置に不感脂化処理槽528が形成されている。また、処理タンク122には、現像槽124の上流側(平版刷版10の搬送方向の上流側)に挿入部134のスペースが設けられ、不感脂化処理槽528の下流側に乾燥部120のスペースが形成されている。
- [0263] この平版刷版10の水洗部617は、一對のニップローラである搬送ローラ672、674によって平版刷版10を大気中で略水平の搬送路上を搬送しながら、画像が顕在化された平版刷版10に対して、水洗水を平版刷版10の表裏の各全面に噴出して現像液を洗い落とす。
- [0264] この水洗部617では、搬送路の上方に、洗浄液(ここでは現像液を洗浄する液体と酸素遮断用の液体とを兼ねた水)を各ノズルから噴射する液体シャワーバー670を設置する。なお、この液体シャワーバー670から噴射されて平版刷版10上へ供給された液体は、平版刷版10の表面全体に広がって搬送方向下流側の搬送ローラ672、674で絞り落とされることになる。
- [0265] 受け皿部材628は、平版刷版10上から絞り落とされ又は平版刷版10の両側からこぼれ落ちた液体を受けるため、受け皿部材628を設置する。受け皿部材628は、搬送路の下側に、露光位置を挟む2組の搬送ローラ672、674を配置した所定範囲を含む一回り大きな範囲をカバーするように配置される。
- [0266] また、この水洗部617では、搬送路の下方に液体シャワーバー671を設置し、この液体シャワーバー671の多数のノズル孔から洗浄液を噴射して平版刷版10の裏面から現像液を洗い流す。この水洗部617では、現像液を洗い流すのに用いた洗浄液が受け皿部材628内へ流れ込むように構成する。なお、この受け皿部材628と、液体シャワーバー670、671との間には、図示しないが、フィルタ、ポンプ及びヒータを備えた液体循環管路を設置する。

- [0267] 上述のようにして水洗部617において、画像が顕在化された画像記録層からアルカリ等の現像液が洗浄された平版刷版10は、搬送路上を搬送されて保護層形成及び後露光処理部618へ送り出される。
- [0268] 前述のように、平版刷版10の画像記録層に対して露光処理をしてラジカル光重合によってポリマー化させて潜像を形成する。平版刷版に対してアルカリ現像液に浸漬した状態でブラシローラによって潜像が形成された画像記録層における未露光の部分除去して露光された画像記録層部分だけを残すことにより画像を顕在化する。水洗部617で平版刷版10はアルカリ等の現像液を洗浄される。この保護層形成及び後露光処理部618は、平版刷版10に対して、保護層を形成する処理の際中に後露光処理を行う。
- [0269] この保護層形成及び後露光処理部618では、保護層を形成する処理として、画像が顕在化された画像記録層の全面にガム液を塗布してからガム液を乾燥させて保護層を形成する。
- [0270] これと共に、保護層形成及び後露光処理部618では、保護層形成の処理におけるガム液を塗布してからガム液を乾燥させるまでの間の、ガム液の溶媒を含む成分が酸素を遮断する機能を利用し、空気中の酸素が画像記録層内に入り込まない状態にする。これにより所要の少ない光量で全面露光する、後露光処理を実行する。
- [0271] この保護層形成及び後露光処理部618で後露光処理を行うのは、耐刷性を向上させるためである。すなわち、平版刷版10は、露光処理後に現像処理されることにより画像記録層におけるポリマー化した部分だけがアルミニウム支持体上に残って画像が形成されることになる。このとき、現像処理後の平版刷版10では、アルミニウム支持体上に画像を形成するように残っている画像記録層の部分が十分にポリマー化されているとは限らず、画像記録層の部分におけるアルミニウム支持体側の一部にポリマー化が不十分な所が残っている場合がある。
- [0272] そこで、保護層形成及び後露光処理部618では、後露光処理によって、平版刷版10の全面を、画像記録層の感光領域の波長を有する光で均等に露光する。これにより、アルミニウム支持体上に画像を形成するように残っている画像記録層の部分を全体に渡って十分にポリマー化することで硬化させることにより、耐刷性を向上させる

ことができる。

- [0273] 図18及び図19に示すように、保護層形成及び後露光処理部618は、大気中を搬送する略水平の搬送路上を搬送されている画像が顕在化され水洗された平版刷版10に対して、ガム液を平版刷版10の表裏の各全面に噴出して所定厚さのガム液の膜を作り、平版刷版10の表面をガム液の膜が覆った酸素遮断状態で後露光処理を行う。このように、平版刷版10の耐刷性を向上するようにしている。保護層形成及び後露光処理部618は、平版刷版10に保護層を形成する構成と、平版刷版10の表面をガム液で覆って酸素遮断状態とする構成とを兼用することにより、部品点数を削減して構成を簡素化する。
- [0274] 図18及び図19に示す保護層形成及び後露光処理部618におけるガム液塗布部分では、平版刷版10を大気中で搬送する搬送路上で後露光処理を行う。このため、後露光位置前後の各所定位置に一对のニップローラである搬送ローラ512、514を配置する。
- [0275] 各搬送ローラ512、514は、これら搬送ローラ512、514の間に平版刷版10を挟み込んだ状態で、一方の搬送ローラ512又は514を図示しない駆動源であるモータ等で回転駆動することにより、平版刷版10を搬送する。なお、これら搬送ローラ512、514は、共にフリーローラとしてもよい。又は、平版刷版10の表面に転接するローラだけにしてこれをフリーローラとし、これらの他に、平版刷版10を搬送するための駆動源で回転駆動されるニップローラを装着してしても良い。
- [0276] 2組の搬送ローラ512、514の間に設定された後露光位置には、搬送される平版刷版10の画像記録層側の表面から所定距離(ここでは、略1mmから略3mmに設定する)をおいた位置に、光照射ユニット520を構成するための透明な部材として構成された露光補助部材516を配置する。ここで、実際に実験した結果、後述するように平版刷版10上にガム液供給ユニットである液体シャワーバー526によってガム液を供給したところ、粘性の高いガム液の表面張力の作用によって、平版刷版10の端部に至るまで、平版刷版10の表面に平均的に広がった厚さ略1mmから略3mmのガム液の層ができることを確認した。
- [0277] よって、この保護層形成及び後露光処理部618では、平版刷版10と光照射ユニッ

ト520を構成するための露光補助部材516の底面との間にガム液の層だけができて空気が入り込まない状態に設定する。このため、ガム液供給ユニットである液体シャワーバー526からガム液を供給して、平版刷版10上にガム液の層ができるようにしたとき、このガム液の層の厚さに等しい距離か又はこれより短い距離となるように平版刷版10と露光補助部材516の底面との間の距離を設定する。

[0278] この露光補助部材516は、レーザービームの入射面と出射面(底面)とを平面に仕上げた、透明なガラス又はプラスチック等の材料を矩形板状(直方体状)に形成したものである。なお、この露光補助部材516は、レンズとしての機能を持つように構成しても良い。

[0279] この保護層形成及び後露光処理部618の光照射ユニット520では、上述のように構成した露光補助部材516を用いる。これにより、平版刷版10上にのる比較的粘性が高いガム液の層の表面に凹凸ができていても、このガム液の層の表面に露光補助部材516が被さってガム液の層の表面を平面化できる。また、露光補助部材516は、その表面が平面であるので、この表面に入射した光を部分的な光量の偏りが起こらないように平均的に平版刷版10の画像記録層に照射させて良好に後露光処理することができる。

[0280] また、図18に示すように、露光補助部材516の直下に当たる搬送される平版刷版10の下側(裏側)には、ガイドローラ540(平版刷版10の下面に摺接してガイドするガイド部材で代用しても良い)を装着する。ガイドローラ540は、平版刷版10の裏面に転接して支持することにより平版刷版10にノズルから噴射されたガム液が当たって振動を生じることを防止する。このガイドローラ540を配置した場合には、液体シャワーバー526のノズルから噴射されたガム液を受けているときに平版刷版10に振動を生じることを抑制した状態で後露光処理することができる。

[0281] この保護層形成及び後露光処理部618では、露光補助部材516を介して後露光処理するために、後露光用の光照射ユニット520を設ける。この光照射ユニット520は、例えば、複数の発光ダイオード(LED、ここでは、紫外線を発光する紫外線LED)520Aを、例えば千鳥格子状等の高い密度で配置されるように集めて構成した光源であるLEDアレイ光源で構成する。複数の発光ダイオード520Aは、平版刷版10の

画像記録層にラジカル光重合反応を起こさせるのに適した感光用の波長の光(赤外線、可視光線又は紫外線等の所定の波長を有する光)を発光する

- [0282] この保護層形成及び後露光処理部618では、光照射ユニット520を構成するための各LED520Aを、図18及び図19に示すように、露光補助部材516の上面部分に埋め込むようにして設置する。なお、複数のLED520Aを設けたLEDアレイ光源を、露光補助部材516と別体に構成しても良い。また、LED520Aを用いる事で、他の光源に比べて使用寿命を飛躍的に延ばす事が出来る。
- [0283] なお、光照射ユニット520は、感光用の波長の光を発光する面光源であるエレクトロルミネセンス(EL:Electro Luminescence)素子で構成しても良い。
- [0284] この保護層形成及び後露光処理部618では、搬送路の上方に、ガム液供給ユニットとしての液体シャワーバー526を設置する。この液体シャワーバー526は、露光補助部材516とこれより搬送方向上流側に配置された搬送ローラ512、514との間の所定位置に、搬送方向に直交する方向に向けて、平版刷版10の幅方向全体に渡る範囲に対応してガム液を噴射するように配置する。
- [0285] この液体シャワーバー526は、例えば、円筒形に形成し、その平版刷版10に向けた周側面に等間隔で多数のノズル孔が列状に配置され、この液体シャワーバー526の内部に供給されたガム液を各ノズルから噴射して、平版刷版10の表面に略均等な薄膜状のガム液の層を作る。
- [0286] すなわち、この液体シャワーバー526から噴射されて平版刷版10上へ供給されたガム液は、平版刷版10の表面全体に広がって、余分なものが端部から流れ落ちる。これにより、そのガム液の粘性と表面張力によって略均等な薄膜状のガム液の層を作る。
- [0287] このように平版刷版10上に供給されたガム液によりできた略均等な薄膜状のガム液の層は、平版刷版10と共に搬送されて、露光補助部材516の位置に至り、露光補助部材516と平版刷版10との間を満たすように入り込む。ガム液の層は、露光補助部材516と平版刷版10との間の隙間に空気の泡を残すことなく十分に埋め尽くし、ガム液の溶媒を含む成分の作用により後露光処理用の酸素遮断状態を作り出す。
- [0288] なお、ここで用いるガム液は、平版刷版10を後露光するための光ビームが透過可

能なものを用いる。例えば、ここで用いるガム液は、富士フイルム株式会社製の、商品名「PS-PLATE FINISHING GUM」品番「FP-2W」を使用することができる。

[0289] この平版刷版10上に作られた略均等な薄膜状のガム液の層は、平版刷版10と共に搬送されて露光補助部材516の位置を離れ、搬送方向下流側の搬送ローラ512、514によって、所定量の薄膜を残すように絞り落とされる。

[0290] このように平版刷版10上から絞り落とされ又は平版刷版10の両側からこぼれ落ちたガム液を受けるため、搬送路の下側に、露光位置を挟む2組の搬送ローラ512、514を配置した所定範囲を含む一回り大きな範囲をカバーする不感脂化处理槽528が設置される。

[0291] また、この不感脂化处理槽528と、液体シャワーバー526との間には、液体循環管路30を設置する。この一連の液体循環管路30を構成する管部材32との液体シャワーバー526との間には、フィルタ34及びポンプ36と、必要に応じてヒータ538を配置する。

[0292] この液体循環管路30は、不感脂化处理槽528の底面に開口した取液口から導入したガム液を、管部材32を通してフィルタ34へ送ってろ過してからポンプ36へ送る。

[0293] このポンプ36は、フィルタ34側から吸引したガム液を加圧して、必要に応じてヒータ38へ送って所定温度に加熱してから、液体シャワーバー526へ供給し、そのノズルから所定の流量で噴射させる。なお、この液体循環管路30で液体シャワーバー526へ供給する新しいガム液は、平版刷版10の処理量に応じて図示しない供給ユニットによって不感脂化处理槽528に供給される。

[0294] 次に、上述のように構成した図18及び図19に示す平版刷版用の保護層形成及び後露光処理部618における、平版刷版の後露光動作について説明する。

[0295] この保護層形成及び後露光処理部618では、現像処理及び水洗処理後の平版刷版10が搬送路上を搬送されて保護層形成及び後露光処理部618へ搬入される。この搬入された平版刷版10は、搬送路上流側に配置された一対の搬送ローラ512、514の間に挟持されて搬送される。これにより、液体シャワーバー526の下でノズルから噴射されたガム液が平版刷版10の表面上に供給されて平版刷版10の表面にガム

液の膜を形成する。

- [0296] この平版刷版10は、さらに搬送されて、露光補助部材516の下の後露光位置に至る。このとき、点灯制御ユニットによって、光照射ユニット520であるLED520Aが点灯される。さらに、平版刷版10上にあるガム液の層は、露光補助部材516に押し延べられる。平版刷版10と露光補助部材516との間の隙間空間内にガム液が充満し、かつ空気の泡等が存在しない状態とされる。
- [0297] この保護層形成及び後露光処理部618では、平版刷版10を搬送しながら、点灯された千鳥格子状に配置された複数のLED520Aで構成したLEDアレイ光源が平版刷版10の幅方向全幅に渡りかつ搬送方向に所定の長さを持つ所定範囲をいわゆる面露光状態で露光する。これにより、平版刷版10の画像記録層全面を平均的に後露光処理する。
- [0298] この保護層形成及び後露光処理部618では、露光補助部材516のある後露光位置から搬送方向下流側の搬送ローラ512、514の位置まで平版刷版10が搬送される間、平版刷版10の画像記録層がガム液に被われて空気中の酸素から遮断された状態を維持する。これにより、画像記録層において、酸素による重合阻害の影響を受けることなく少ない露光量でラジカル重合反応を残らず進めて十分な反応を実現し、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の十分な耐刷性を確保できる。
- [0299] また、このように平版刷版10に対して後露光処理する場合には、平版刷版10の原版に変調されたレーザー光を投影して平版刷版10の原版の画像記録層に直接画像を記録して潜像を形成するレーザー露光処理を行う際に、この潜像形成の為の露光量を少なく抑える事ができる。このため、記録光としてのレーザー光の出力を低パワーにして画像形成をすることが可能となる。
- [0300] この保護層形成及び後露光処理部618では、後露光処理のため点灯したLED520Aを、光源点灯制御回路23の制御により、版端検出センサ21が平版刷版10の搬送方向後端を検知したときからタイマで計測して消灯用所定待機時間を経過した時点で消灯させる。
- [0301] 前述のように露光補助部材516がある後露光位置で後露光処理された平版刷版1

0は、搬送ローラ512、514で表面に所定量のガム液の膜が残るように絞られ、その搬送方向下流側にある乾燥部120へ搬出される。

- [0302] この保護層形成及び後露光処理部618では、ガム液を、液体循環系のフィルタ34とポンプ36とを用いて液に紛れ込むゴミを除去しながら循環して使用する。この保護層形成及び後露光処理部618では、液体循環系のフィルタ34を通すことによりゴミを除去したガム液を平版刷版10の画像記録層に供給する。これにより、ガム液中に浮遊するゴミにより後露光されない部分が発生することを防止できる。
- [0303] この保護層形成及び後露光処理部618では、大気中を搬送する搬送路上を、画像記録層を上に向けて搬送されている平版刷版10に対して後露光用の光を上方から照射して後露光処理できる。LEDアレイ光源を、平版刷版10上のガム液及びガム液を流下させる液体シャワーバー526よりも高い位置に配置する。ガム液が跳ねが有ったり又は万一ガム液漏れが有った場合でも、LEDアレイ光源がガム液で濡れることを防止できる。
- [0304] また、この図18及び図19に示す保護層形成及び後露光処理部618では、図示しないスプレーパイプの吐出孔から平版刷版10の裏面へ向けてガム液を吐出して、平版刷版10の裏面にガム液を塗布するようにしても良い。また図示しないが、スプレーパイプに換えて、吐出したガム液に平版刷版10が接触しながら移動することにより平版刷版10の裏面にガム液を塗布する吐出ユニット等を用いても良い。
- [0305] この保護層形成及び後露光処理部618では、図示しないが、搬送ローラ512に転接する洗浄ローラへ所定のタイミングで洗浄スプレーから洗浄水を滴下する。これにより、洗浄水を搬送ローラ512の周面に均一に拡散させて、搬送ローラ512、514の周面からガム液を洗い流す。搬送ローラ512、514の周面にガム液が固着して平版刷版10を損傷させてしまうことを防止する。
- [0306] 次に、この平版刷版の現像装置に用いる、平版刷版用の露光用器具を備えた保護層形成及び後露光処理部618に係わる他の構成例について主に図20により説明する。この図20に示す平版刷版用の保護層形成及び後露光処理部618では、露光補助部材516に対してガム液を平版刷版10上に供給するユニットを一体的に構成する。なお、露光補助部材516の構成は、第2実施の形態と同様である(図4、及び図5

参照)。

- [0307] この後露光に用いる器具である露光補助部材516は、管部材32から送給されたガム液を液体供給路の導液溝17Aから液体供給用開口を通じて、平版刷版10上へ所要量ずつ流下させる。
- [0308] この図20に示す保護層形成及び後露光処理部618では、後露光処理を行う際に、搬送ローラ512、514とガイドローラ540とによって搬送されている平版刷版10の画像記録層上に対し、露光補助部材516の搬送方向上流側にある液体供給用開口から、平版刷版10の幅方向全長に渡って略均等に所要量のガム液を流下させる。
- [0309] すると、露光補助部材516の液体供給用開口から流下したガム液は、平版刷版10の搬送動作と相俟って、平版刷版10の画像記録層と露光補助部材516の下面全体との間に充填され、空気の泡が混入しないように満たされる。この後露光に用いる器具としての液体供給ユニットを備えた露光補助部材516では、露光補助部材516における搬送方向上流側にある液体供給用開口からガム液を流下する。これにより、ガム液が直ちに平版刷版10と露光補助部材516の下面全体との間に広がって迅速に充填する。このため、比較的少ない量のガム液で効率良く平版刷版10と露光補助部材516との間にガム液を充填させることができる。しかも平版刷版10と露光補助部材516との間に充填されてできたガム液の層の厚さを比較的容易に厚くすることができる。
- [0310] このとき、平版刷版10上に供給されたガム液は、後露光位置より搬送方向上流側の搬送ローラ512、514と、後露光位置より搬送方向下流側の搬送ローラ512、514との間に広がるように流れてガム液の層を形成する。
- [0311] この平版刷版用の保護層形成及び後露光処理部618では、露光補助部材516と平版刷版10との間にガム液を満たした状態で、搬送ローラ512、514によって平版刷版10を搬送しながら、光照射ユニット520から出射された後露光用の光を、後露光位置の所定範囲でいわゆる面露光して後露光処理をする。
- [0312] このとき、現像処理済みの平版刷版10の画像記録層は、ガム液に被われて空気中の酸素から遮断された状態が維持される。これにより、現像処理済みの画像記録層において、酸素による重合阻害の影響を受けることなくラジカル重合反応を残らず進

めるようにして、画像を形成している画像記録層全体をポリマー化して硬化し、平版刷版10の耐刷性を向上することができる。

- [0313] なお、上述した図20に示す平版刷版用の保護層形成及び後露光処理部618における以上説明した以外の構成、作用及び効果は前述した図18及び図19に示す保護層形成及び後露光処理部と同様であるので、その説明を省略する。
- [0314] 次に、保護層形成及び後露光処理部に係わる他の構成例について図21により説明する。この図21に示す保護層形成及び後露光処理部618では、搬送路上の後露光位置よりも搬送方向上流側に直近の搬送ローラ512が、ガム液を平版刷版10の画像記録層上に供給する。また、この図21に示す保護層形成及び後露光処理部618では、平版刷版10上にガム液の層を形成している状態で、露光補助部材を介することなく直接的に光照射ユニット520で後露光処理を行う。
- [0315] 後露光位置よりも搬送方向上流側に直近の搬送ローラ512における搬送ローラ512の中心を通る鉛直線よりも搬送方向下流側の外周面上に液体シャワーバー526からガム液を流下させる。
- [0316] また、この保護層形成及び後露光処理部618では、後露光位置よりも搬送方向上流側に直近の搬送ローラ512の外周面に沿ってガム液を平均的に流すようにガイドする流下ガイド部材15を設置する。
- [0317] 図21に示す保護層形成及び後露光処理部618では、液体シャワーバー526から流下したガム液を導入ガイド部15Bと補助流下ガイド部材19とで受けて、搬送ローラ512の外周面と円弧状のガイド部分15Aとの間に導入し、これらの間を搬送ローラ512の外周面に沿うように流して、平版刷版10上へ導く。
- [0318] このように平版刷版10上に導かれたガム液は、排出ガイド部15Cにガイドされて平版刷版10の画像記録層全面上に平均的に供給され、後露光位置より搬送方向上流側と搬送方向下流側とにそれぞれ配置された搬送ローラ512、514との間に広がるように流れて、表面張力によりガム液の層を形成する状態となる。
- [0319] また、保護層形成及び後露光処理部618では、図23に示すように、後露光位置よりも搬送方向上流側で、直近の搬送ローラ512における搬送ローラ512の中心を通る鉛直線よりも搬送方向上流側の外周面上に液体シャワーバー526からガム液を流

下させるようにしても良い。

[0320] この場合には、後露光位置よりも搬送方向上流側に、直近の搬送ローラ512における搬送方向上流側に向いている外周面に沿ってガム液を平均的に流すようにガイドする流下ガイド部材529を設置する。

[0321] この図23に示す流下ガイド部材529を設けた保護層形成及び後露光処理部618では、液体シャワーバー526から流下した粘性を有するガム液を導入ガイド部529Bと搬送ローラ512の外周面との間に受けて、この搬送ローラ512の外周面と円弧状のガイド部分529Aとの間に導入し、搬送ローラ512が平版刷版10を搬送する。このため、図23の矢印方向に搬送ローラ512が回転する際に、ガム液の粘性によってガム液が搬送ローラ512の外周面と一体的に回転するよう運ばれて平版刷版10上へ導かれる。

[0322] このように平版刷版10上に導かれたガム液は、搬送ローラ512が平版刷版10に転接する際に画像記録層全面上に平均的に押し広げられて、後露光位置より搬送方向上流側と搬送方向下流側とにそれぞれ配置された搬送ローラ512、514との間に広がるガム液の層を形成する。

[0323] 前述のように構成した場合には、図21に示すように、後露光位置より搬送方向上流側の直近に配置された搬送ローラ512と、後露光位置より搬送方向下流側の直近に配置された搬送ローラ512との間に、液体シャワーバー526からガム液を流下させるためのスペースを設けずに済む。これにより、後露光位置より搬送方向上流側の直近に配置された搬送ローラ512と、後露光位置より搬送方向下流側の直近に配置された搬送ローラ512との間を接近させて配置できる。このため、保護層形成及び後露光処理部618を備えた平版刷版の現像装置を小型化することができる。

[0324] また、この保護層形成及び後露光処理部618では、後露光位置の上方に光照射ユニット520としての複数のLED520Aを設けたLEDアレイ光源が配置され、LED520Aからガム液の薄い酸素遮断用の層を介して平版刷版10の現像処理済みの画像記録層に、後露光用の光を照射する。

[0325] この保護層形成及び後露光処理部618では、平版刷版10の現像処理済みの画像記録層に形成される酸素遮断用のガム液の層の表面に多少の凹凸が発生しても、L

ED520Aから光を照射して後露光処理を行う上で支障がない。これは、記録用のレーザービームを平版刷版10の画像記録層に合焦させる場合と異なり、平版刷版10の現像処理済みの画像記録層に後露光用の所定波長の光を照射してラジカル重合反応を生じさせることができれば良いので、酸素遮断用ガム液層の表面にできた凹凸で、後露光用の光が散乱してもラジカル重合反応を生じさせることに影響が無いためである。

- [0326] なお、前述した図18及び図19に示す保護層形成及び後露光処理部618でも、露光補助部材516を省略してLED520Aから酸素遮断用のガム液の層を介して平版刷版10の現像処理済みの画像記録層に後露光用の光を照射するように構成しても良い。
- [0327] さらに、図21に示す流下ガイド部材15を設けた保護層形成及び後露光処理部618では、液体シャワーバー526から搬送ローラ512にガム液が流下される際に流下したガム液が跳ね返って光照射ユニット520としてのLED520Aに付着することを流下ガイド部材15によって防止できる。
- [0328] なお、この図21(図23に示す構成に代えたものも同じ)に示す保護層形成及び後露光処理部618における以上説明した以外の構成、作用及び効果は、前述した図18及び図19に示す保護層形成及び後露光処理部618と同様であるので、その説明を省略する。
- [0329] 図22に示すように、この平版刷版の現像装置では、保護層形成及び後露光処理部618において、平版刷版10の表裏面にガム液を塗布して表裏面にガム液が所定量残った状態(ガム液が薄膜として残った状態)で乾燥部120へ送る。
- [0330] この保護層形成及び後露光処理部618では、ガム液を塗布するための不感脂化处理槽528を設けた部分と乾燥部120との間に、仕切り板182が設けられている。この仕切り板182は、平版刷版10の搬送路の上方に、処理タンク122の上端と対向するように配置されており、これにより、ガム液を塗布するための不感脂化处理槽528を設けた部分と乾燥部120の間にスリット状の挿通口184が形成されている。なお、仕切り板182は、二重構造となっており、これにより、挿通口184の乾燥部120側に溝状の通気路が形成される。乾燥部120内の空気がこの通気路内に入り込むことによ

り、乾燥部120内の空気が挿通口184からガム液を塗布するための不感脂化处理槽528を設けた部分内に入り込んでしまうのを防止している。

[0331] 乾燥部120内には、挿通口184の近傍に、平版刷版10を支持する支持ローラ186が配設され、また、平版刷版10の搬送方向の中央部及び、排出口188の近傍には、搬送ローラ対190及び搬送ローラ対192が配設されている。平版刷版10は、支持ローラ186及び搬送ローラ対190、192によって乾燥部120内を搬送される。

[0332] 支持ローラ186と搬送ローラ対190との間、及び搬送ローラ対190と搬送ローラ対192との間には、平版刷版10の搬送路を挟んで対でダクト194、196が配設されている。ダクト194、196は、長手方向が平版刷版10の幅方向に沿って配設されており、平版刷版10の搬送路に対向する面にスリット孔198が設けられている。

[0333] ダクト194、196は、図示しない乾燥風発生ユニットによって発生された乾燥風が、長手方向の一端側から供給されると、この乾燥風をスリット孔198から平版刷版10の搬送路へ向けて吐出し、平版刷版10に吹き付ける。これにより、平版刷版10は、表裏面に塗布されているガム液が乾燥され、保護膜が形成される。

[0334] この保護層形成及び後露光処理部618では、後露光処理を、平版刷版10の現像された表面に親水層保護の為にガム液を塗布してから乾燥し終えるまでの間に、ガム液の溶媒を含む成分によって空気中の酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態にして行う。

[0335] このため、保護層形成及び後露光処理部618では、乾燥部120で後露光処理を行い、ガム液を塗布するための不感脂化处理槽528を設けた部分で後露光処理を行わないように構成しても良い。

[0336] 図24に示すように、この場合には、乾燥部120における搬送方向上流側のダクト194に、後露光用の光照射ユニットを設ける。この光照射ユニットは、例えば、ダクト194のスリット孔198を設けた部分に配置した導光体195と、複数の発光ダイオード(LED、ここでは、紫外線を発光する紫外線LED)520Aで構成した光源であるLEDアレイ光源とによって構成する。複数の発光ダイオード520Aは、平版刷版10の画像記録層にラジカル光重合反応を起こさせるのに適した感光用の波長の光(赤外線、可視光線又は紫外線等の所定の波長を有する光)を発光する。

- [0337] この導光体195は、出射端部を、スリット孔198近くを搬送される平版刷版10の画像記録層に臨ませ、入射端部をスリット孔198から噴射される熱風の熱気が及ばない位置に臨ませるように配置する。さらに、導光体195の入射端部には、発光ダイオード520Aで構成したLEDアレイ光源を配置する。
- [0338] このように構成することにより、発光ダイオード520Aがダクト194のスリット孔198から噴射される熱気によって劣化することを防止できる。
- [0339] 次に、上述のように構成した本実施の形態に係わる平版刷版の現像装置の作用及び動作について説明する。なお、第7実施の形態と同様の構成については説明を省略する。
- [0340] 現像処理を終えて現像槽124から送り出される平版刷版10は、搬送ローラ対152によって水洗部617へ送られる。このとき、搬送ローラ対152は、平版刷版10の表裏面に付着している現像液を絞り落とす。
- [0341] 水洗部617では、この平版刷版10を搬送ローラ672、674によって挟持して略水平方向に搬送しながら、液体シャワーバー670、液体シャワーバー671から水洗水を噴出して、平版刷版10の表裏面に残っている現像液を洗い落とし、図示しない乾燥器で乾燥してから、この平版刷版10を保護層形成及び後露光処理部618へ送り出す。
- [0342] 保護層形成及び後露光処理部618へ送られた平版刷版10は、搬送ローラ512、514に挟持されて転接されることにより、搬送路上を搬送されて乾燥部120へ送り出される。
- [0343] このとき、保護層形成及び後露光処理部618では、液体シャワーバー526等からガム液を吐出して、平版刷版10の表裏面にガム液を均一に塗布する。搬送ローラ512、514は、平版刷版10を挟持搬送して、余剰となったガム液を平版刷版10の表裏面から絞り落とすことにより、平版刷版10の表裏面にガム液の均一な薄膜を形成する。
- [0344] ガム液が塗布された平版刷版10は、搬送ローラ512、514によって挿通口184から乾燥部120へ送り込まれる。なお、挿通口184にシャッタを設けているときには、平版刷版10の処理開始のタイミング又は平版刷版10がガム液を塗布するための不感脂化处理槽528を設けた部分から送り出されるタイミングで、シャッタを作動させて

、挿通口184を開放する。これにより、平版刷版10の非通過時に乾燥部120の乾燥風が不必要にガム液を塗布するための不感脂化处理槽528を設けた部分へ入り込んで、搬送ローラ512、514にガム液が固着してしまうのを防止する。挿通口184から空気が入り込み、現像部114にまで及んで空気中の炭酸ガスにより現像液が劣化するのを防止する。現像液中の水分や水洗水さらにガム液中の水分が蒸発して挿通口184から出てしまうのを防止している。

[0345] 乾燥部120では、支持ローラ186及び搬送ローラ対190、192によって平版刷版10を搬送しながら、ダクト194、196からこの平版刷版10の表裏面に熱風である乾燥風を吹き付ける。この乾燥部120では、平版刷版10に熱風を吹き付けるので、熱により光重合層の重合度を増加させて耐刷力を向上させることができる。

[0346] この保護層形成及び後露光処理部618では、液体シャワーバー526から噴射したガム液で画像記録層の表面を全体的に覆い、ガム液の溶媒(水分等)及びその他の成分により空気中の酸素を遮断し空気中の酸素が画像記録層内に入り込まないようにした状態で、LED20Aを点灯して後露光処理を行う。

[0347] これにより、平版刷版10は、表面に塗布されているガム液による保護膜が形成されて排出口188から排出される。

[0348] なお、本発明は、上述した実施の形態に限定されるものではなく、本発明の要旨を逸脱しない範囲で、その他種々の構成を取り得ることは勿論である。

符号の説明

- [0349]
- 10 平版刷版
 - 12 搬送ローラ
 - 14 搬送ローラ
 - 15 流下ガイド部材
 - 15A ガイド部分
 - 15B 導入ガイド部
 - 15C 排出ガイド部
 - 16 露光補助部材
 - 16A 部材本体

- 16B 端面側部材
- 16C 端面部材
- 16D 接続端部材
- 17 補助流下ガイド部材
- 17A 導液溝
- 18 ガイド部材
- 20 光照射ユニット
- 20A 発光ダイオード
- 21 版端検出センサ
- 23 光源点灯制御回路
- 25 光源用電源
- 26 液体シャワーバー
- 28 受け皿部材
- 30 液体循環管路
- 32 管部材
- 34 フィルタ
- 36 ポンプ
- 38 ヒータ
- 39 乾燥器
- 40 ガイドローラ
- 100 現像処理部
- 117 水洗部
- 120 乾燥部
- 124 現像槽
- 194 ダクト
- 195 導光体
- 427 液体シャワーバー
- 428 受け皿部材

- 512 搬送ローラ
- 514 搬送ローラ
- 520 光照射ユニット
- 520A 発光ダイオード
- 526 液体シャワーバー
- 528 不感脂化处理槽
- 618 後露光処理槽

請求の範囲

- [1] 支持体の表面にラジカル光重合反応によって潜像が形成される画像記録層を有する平版刷版に対して、画像に対応した露光用の光を照射してラジカル光重合反応を起こさせることにより画像部を固化させた前記潜像を形成し、
- 前記平版刷版の前記潜像が形成された前記画像記録層における前記ラジカル光重合されなかった非画像部を除去する現像処理をし、
- 前記現像処理がされた前記平版刷版の前記表面に前記画像を形成するように残っている前記画像記録層の上を液体の層で覆って酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光で全面露光を行うことにより後露光処理をする、
- 平版刷版の後露光方法。
- [2] 板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層を形成した平版刷版に対する露光処理で画像に対応した露光用の光を照射して画像部を固化させた前記潜像を形成し、前記平版刷版に対する現像処理で前記潜像が形成された前記画像記録層におけるラジカル光重合されなかった非画像部を除去した前記平版刷版に対して光重合層硬化処理を行う、平版刷版の耐刷性向上用の後露光装置であって、
- 前記平版刷版を気体中で搬送する搬送路と、
- 前記搬送路上を搬送されている前記平版刷版の前記表面に前記画像を形成するように残っている前記画像記録層の上に、酸素を遮断するため、前記平版刷版に対して不活性で前記画像記録層にラジカル光重合を起こさせる波長の光を透過可能な液体の層を作るための液体供給ユニットと、
- 前記搬送路上を搬送されている前記平版刷版の全面に対して、前記液体の層を通してラジカル光重合を起こさせる波長の光を照射する光照射ユニットと、
- を有する前記平版刷版の後露光装置。
- [3] 前記光照射ユニットが、発光ダイオード(LED)を有する請求項2に記載の平版刷版の後露光装置。
- [4] さらに、前記搬送路上で前記平版刷版の表面から前記液体を介在させる間隔をあけて配置され、前記光照射ユニットより照射される前記光を透過可能であるように透明

な部材からなり、前記搬送路側の底面が平面で形成されている露光補助部材を有する請求項2に記載の平版刷版の後露光装置。

- [5] 前記露光補助部材は、前記搬送路側の底面に、前記平版刷版の搬送方向上流側の端部で、前記搬送方向に直行する方向に渡る位置に配設された液体供給用開口を有し、前記露光補助部材の外部より供給され前記液体が前記液体供給用開口を介して前記露光補助部材と前記平版刷版の表面の間に供給されるように、前記液体供給ユニットと一体となって形成される請求項4に記載の平版刷版の後露光装置。
- [6] 前記液体供給ユニットは、前記搬送路上で前記光照射ユニットよりも前記平版刷版の搬送方向上流に配置され、前記液体を噴出する液体シャワーバーを有する請求項2に記載の平版刷版の後露光装置。
- [7] さらに、前記搬送路上で前記光照射ユニットよりも前記搬送方向上流側に配置されて前記平版刷版に転接する搬送ローラを有し、
前記液体供給ユニットが、さらに、前記液体シャワーバーから前記搬送ローラに対して流下した前記液体を受ける導入ガイド部と、前記搬送ローラの外周面との間で前記導入ガイド部が受けた前記液体を案内する円弧状のガイド部分と、前記搬送ローラの外周面と前記円弧状のガイド部分との間を流れた前記液体を前記平版刷版上へ導く流下ガイド部材と、を有する請求項6に記載の平版刷版の露光装置。
- [8] さらに、前記液体供給ユニットから供給され、前記平版刷版から流れ落ちた前記液体をろ過して、ろ過した前記液体を前記液体供給ユニットへ供給する液体循環ユニットを有する請求項2に記載の平版刷版の後露光装置。
- [9] 板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層を形成した平版刷版を、前記画像記録層の表面に酸素遮断層が無い状態で露光用の光ビームを照射する露光位置に搬入して露光処理を行う平版刷版の露光装置であって、
前記平版刷版を気体中で搬送する搬送路と、
前記搬送路における前記露光位置に搬送される前記平版刷版の前記表面から液体を介在させる間隔を開けて配置される、透明な部材に露光用の光ビームを透過させる平面が形成された露光補助部材と、

前記搬送路上における前記露光補助部材の搬送方向上流側で、前記露光補助部材と前記平版刷版との間に前記平版刷版に対して不活性で前記露光用の前記光ビームを透過可能な前記液体を充填させる液体供給ユニットと、

を有する前記平版刷版の露光装置。

[10] 前記露光補助部材と、前記平版刷版との距離が、前記平版刷版上に生じる前記液体の層の厚さ以下である請求項9に記載の平版刷版の露光装置。

[11] さらに、前記搬送路上に配置された前記露光補助部材の下方に対応した位置に、前記平版刷版の下面をガイドするガイド部材を有する請求項9又は請求項10に記載の平版刷版の露光装置。

[12] 前記液体供給ユニットが、

前記搬送路上における前記露光補助部材から直近の前記搬送方向上流側に配置されて、前記平版刷版に転接する搬送ローラと、

前記搬送ローラに対して前記液体を流下する液体シャワーバーと、

前記液体シャワーバーから流下した前記液体を導入ガイド部で受け、前記搬送ローラの外周面と円弧状のガイド部分との間に導入し、これらの間を流して前記平版刷版上へ導く流下ガイド部材と、

を有する請求項9乃至請求項11の何れか1項に記載の平版刷版の露光装置。

[13] 搬送される平板状の被露光体に対し、当該被露光体の表面を空気から遮断する液体の層を介して透明な部材部分を配置し、露光用の光ビームが前記透明な部材部分と液体の層とを透過して前記被露光体に照射するようにするための露光用器具であって、

前記透明な部材部分の底面における、前記被露光体の搬送方向上流側に当たる端部で前記被露光体の搬送方向に直交する方向に渡る位置に、液体供給用開口を配設し、

前記透明な部材部分の外部から送給された液体を、液体供給路を通して前記液体供給用開口から、前記露光用器具の透明な部分の底面と前記被露光体との間に供給するように構成した前記露光用器具。

[14] 支持体の表面上に光ラジカル重合反応を利用した画像形成のために画像記録層が

設けられた平版刷版の現像方法であって、

前記画像記録層に画像に対応した露光用の光を照射して潜像が形成された前記平版刷版に対して、前記潜像が形成された前記画像記録層の未露光の部分を前記支持体から除去して前記潜像を顕在化する現像処理をし、

前記現像処理された前記平版刷版の少なくとも前記画像記録層上に液体を供給して前記現像液を洗浄すると共に、前記画像記録層の表面を前記液体で覆った酸素遮断状態で光ラジカル重合反応を開始又は促進する波長の光で全面露光することにより、前記平版刷版の耐刷性を向上する後露光処理を行う、

前記平版刷版の現像方法。

- [15] 板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層が形成された、露光用の光が照射されて前記画像記録層に前記潜像が形成された前記平版刷版を搬入し、前記画像記録層における露光されなかった部分を前記支持体から除去して画像を顕在化する現像部と、

前記画像が顕在化された前記平版刷版を気体中で搬送する搬送路と、

前記搬送路上を搬送されている前記平版刷版に対して、少なくとも前記表面に前記画像を形成するように残っている前記画像記録層の上に付着している前記現像液を洗い流すと共に、前記画像記録層にラジカル光重合を起こさせる波長の光を透過可能なように酸素を遮断する層を作るように、液体を供給する液体供給ユニットと、

前記搬送路上を搬送されている前記平版刷版の前記画像記録層全面に対して、前記液体の層を通してラジカル光重合を起こさせる前記波長の光を照射する光照射ユニットと、

を有する平版刷版の現像装置。

- [16] 前記光照射ユニットが、発光ダイオード(LED)を有する請求項15に記載の平版刷版の現像装置。

- [17] 支持体の表面上に光ラジカル重合反応を利用した画像形成のために画像記録層が設けられた平版刷版の現像方法であって、

前記画像記録層に画像に対応した露光用の光が照射されて潜像が形成された前記平版刷版に対して、前記潜像が形成された前記画像記録層の未露光の部分を前

記支持体から除去して前記潜像を顕在化する現像処理工程と、

前記現像処理工程を終えた前記平版刷版の前記表面に前記画像を形成するように残っている前記画像記録層の上を、親水層を保護する保護層を形成するために塗布されたガム液の層で覆って当該ガム液の溶媒を含む成分が酸素を遮断する状態で、ラジカル光重合を起こさせる波長の光で全面露光を行うことにより前記平版刷版の耐刷性を向上させる保護層形成工程及び後露光処理工程と、

を有する前記平版刷版の現像方法。

- [18] 板状の支持体の表面にラジカル光重合によって潜像が記録される画像記録層が形成された平版刷版に、露光用の光が照射されて前記画像記録層に潜像が形成された前記平版刷版を搬入して、前記画像記録層における露光されなかった部分を前記支持体から除去して画像を顕在化する現像部と、

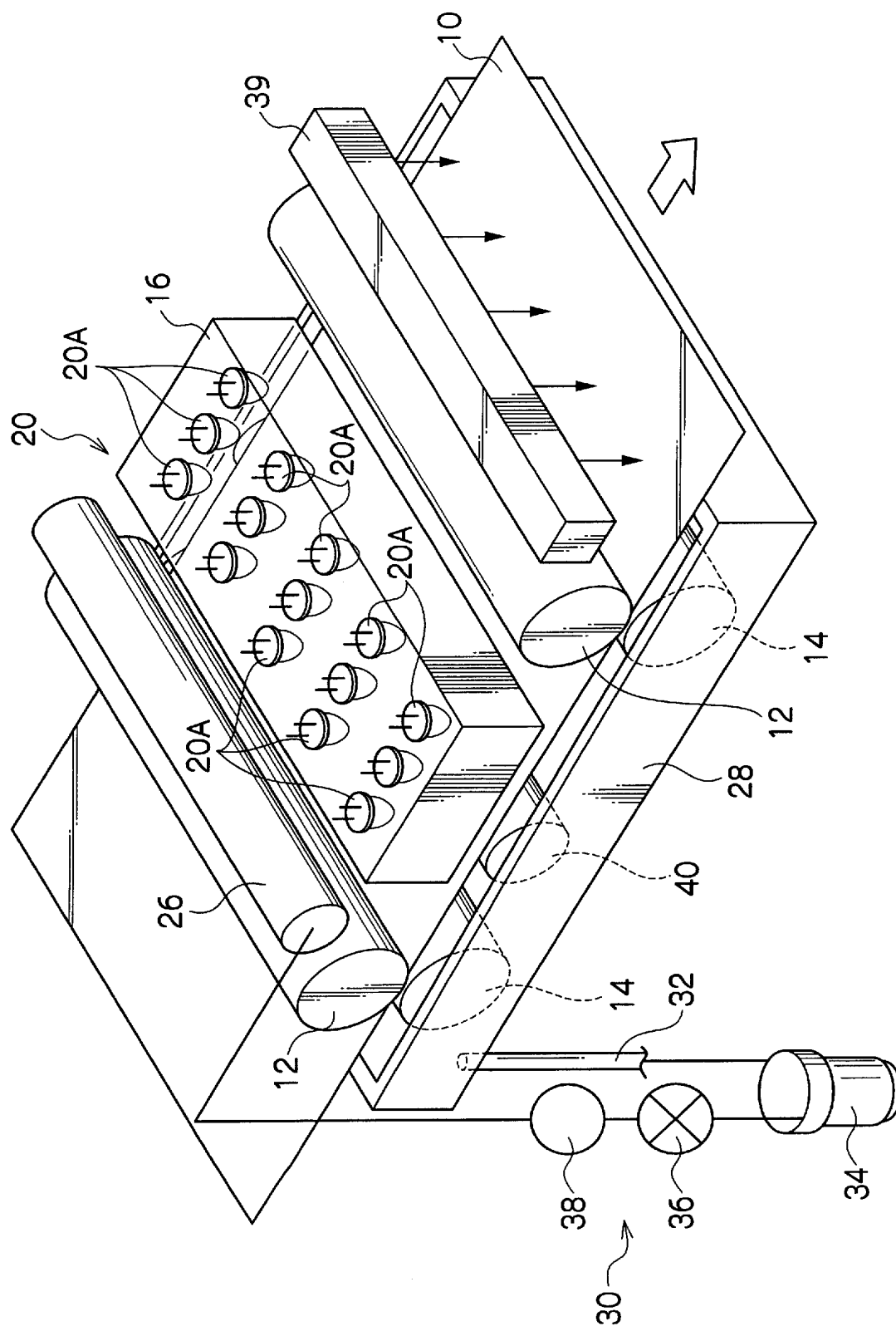
前記画像が顕在化された前記平版刷版を気体中で搬送する搬送路と、

前記搬送路上を搬送されている前記平版刷版に対して、少なくとも前記表面に前記画像を形成するように残っている前記画像記録層の上に親水層を保護する保護層を形成するためのガム液を塗布し、前記ガム液の溶媒を含む成分が前記画像記録層にラジカル光重合を起こさせる波長の光を透過可能であると共に酸素を遮断して空気中の酸素が前記画像記録層内に入り込まないようにした状態で、前記搬送路上を搬送されている前記平版刷版の前記画像記録層全面に対してラジカル光重合を起こさせる波長の光を照射する光照射ユニットと、

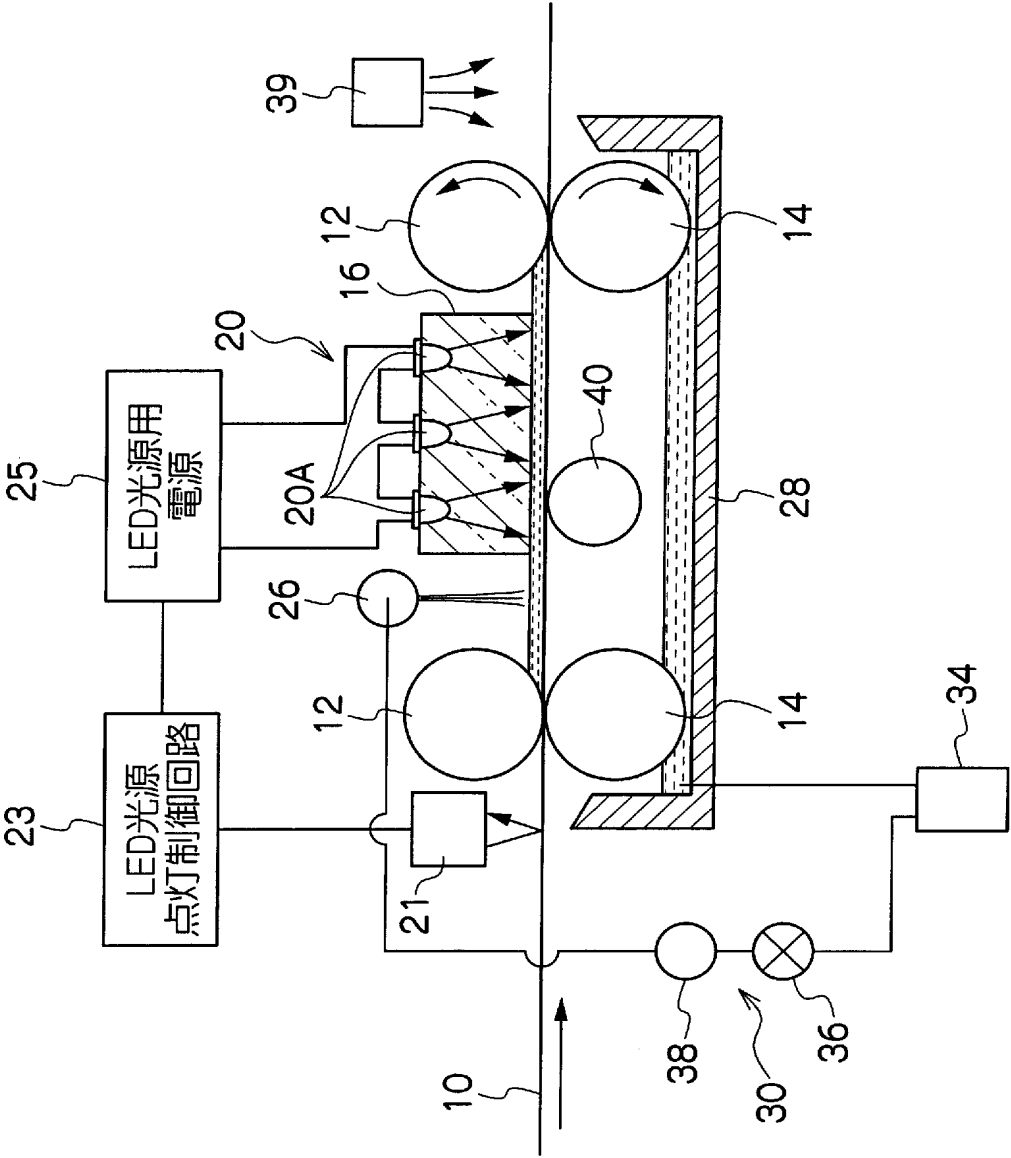
を有する、平版刷版の現像装置。

- [19] 前記光照射ユニットを、発光ダイオード(LED)を有する請求項18に記載の平版刷版の現像装置。

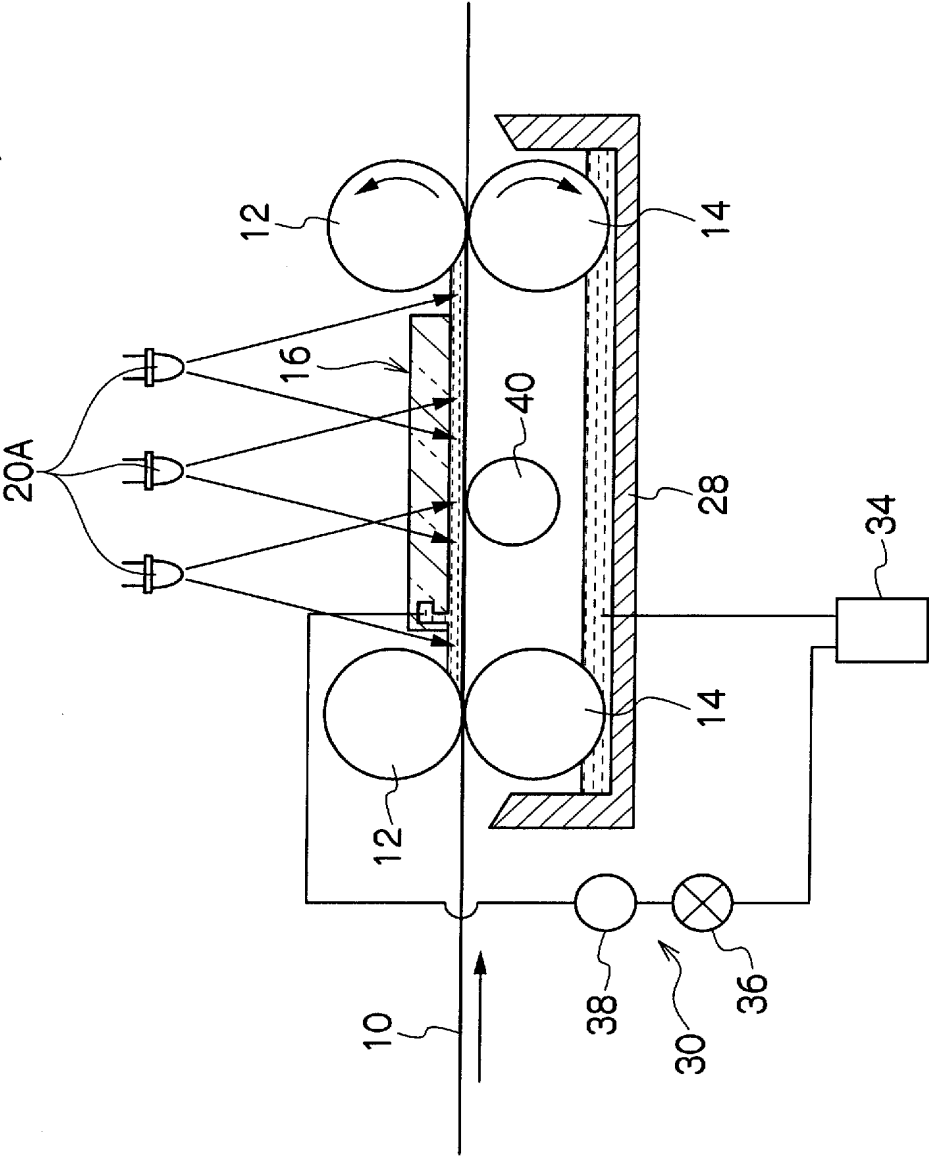
[図1]



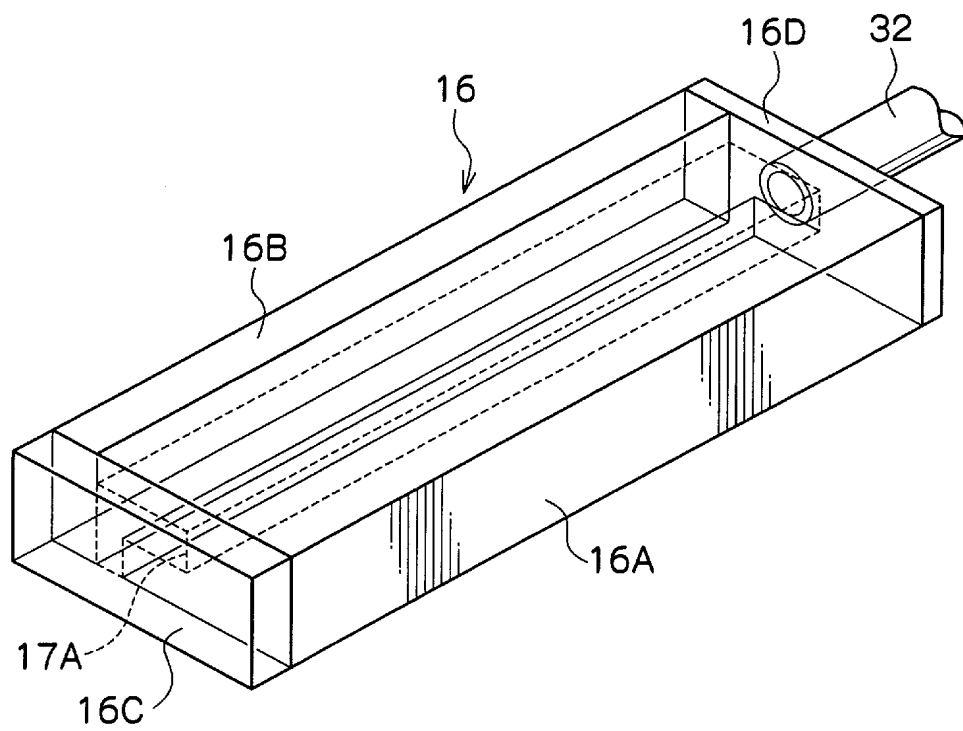
[図2]



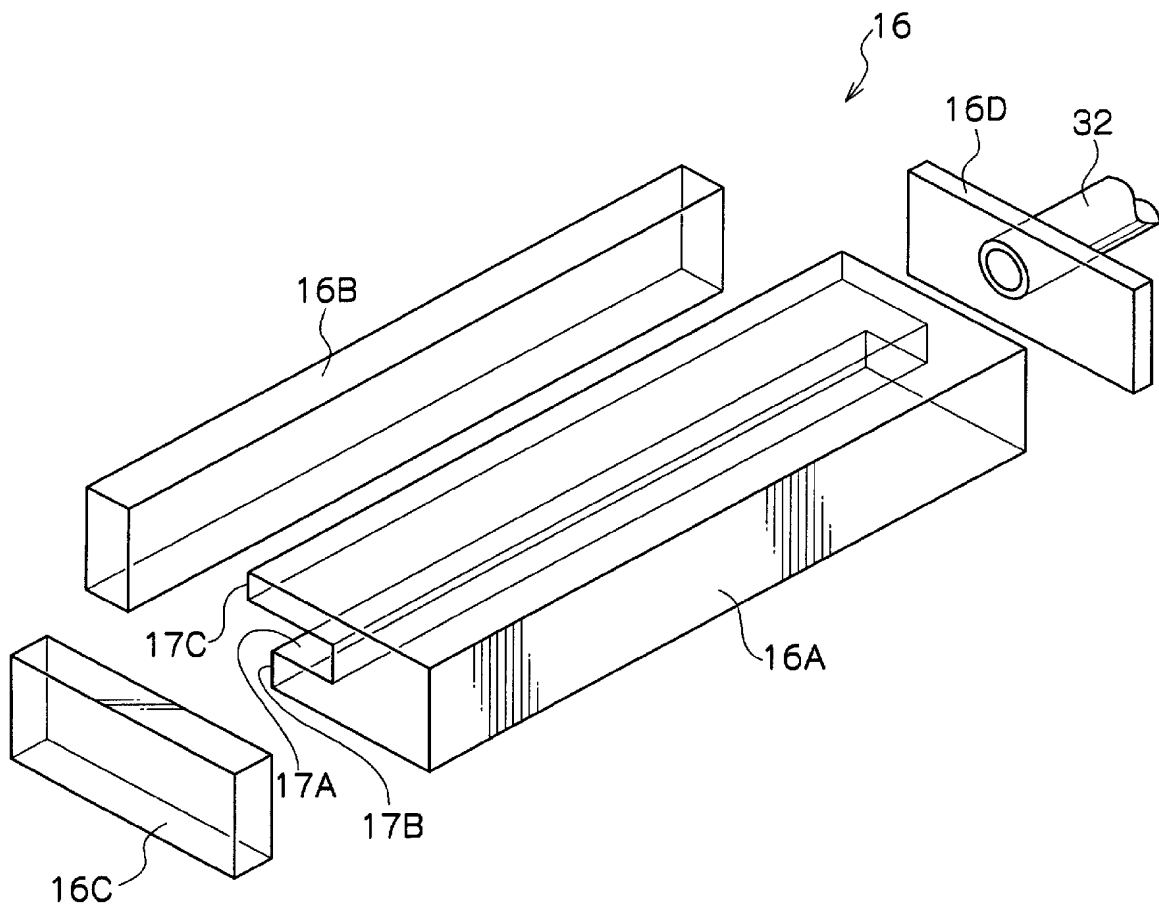
[図3]



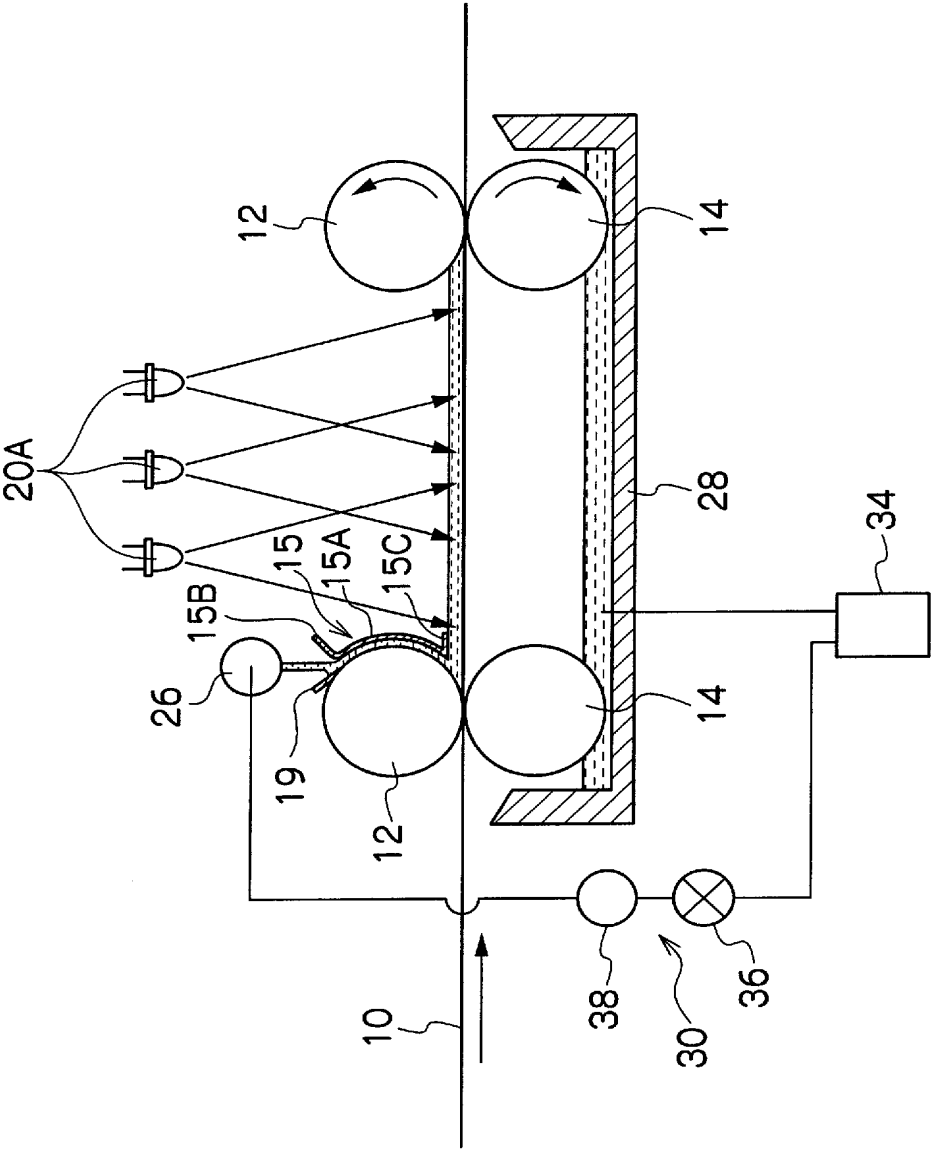
[図4]



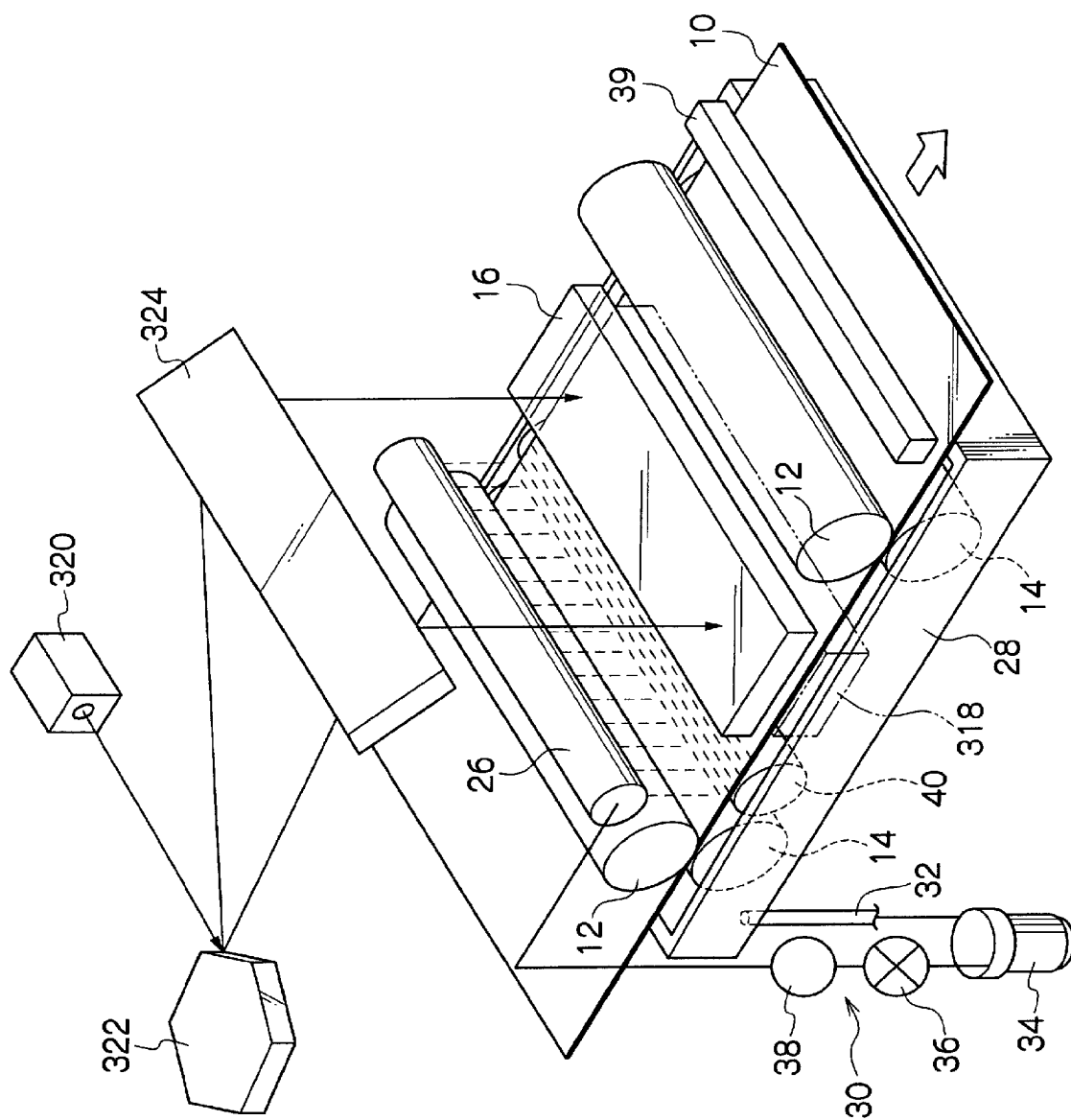
[図5]



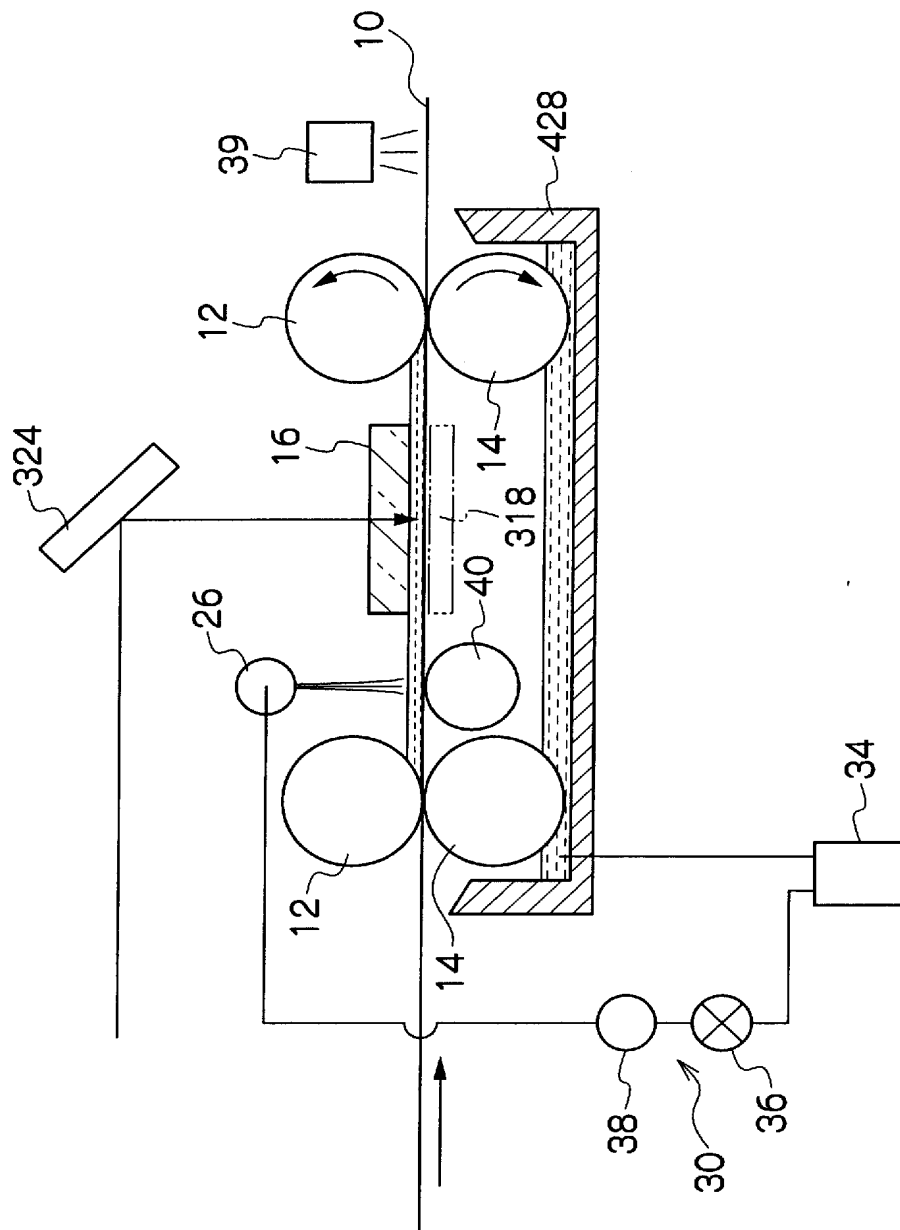
[図6]



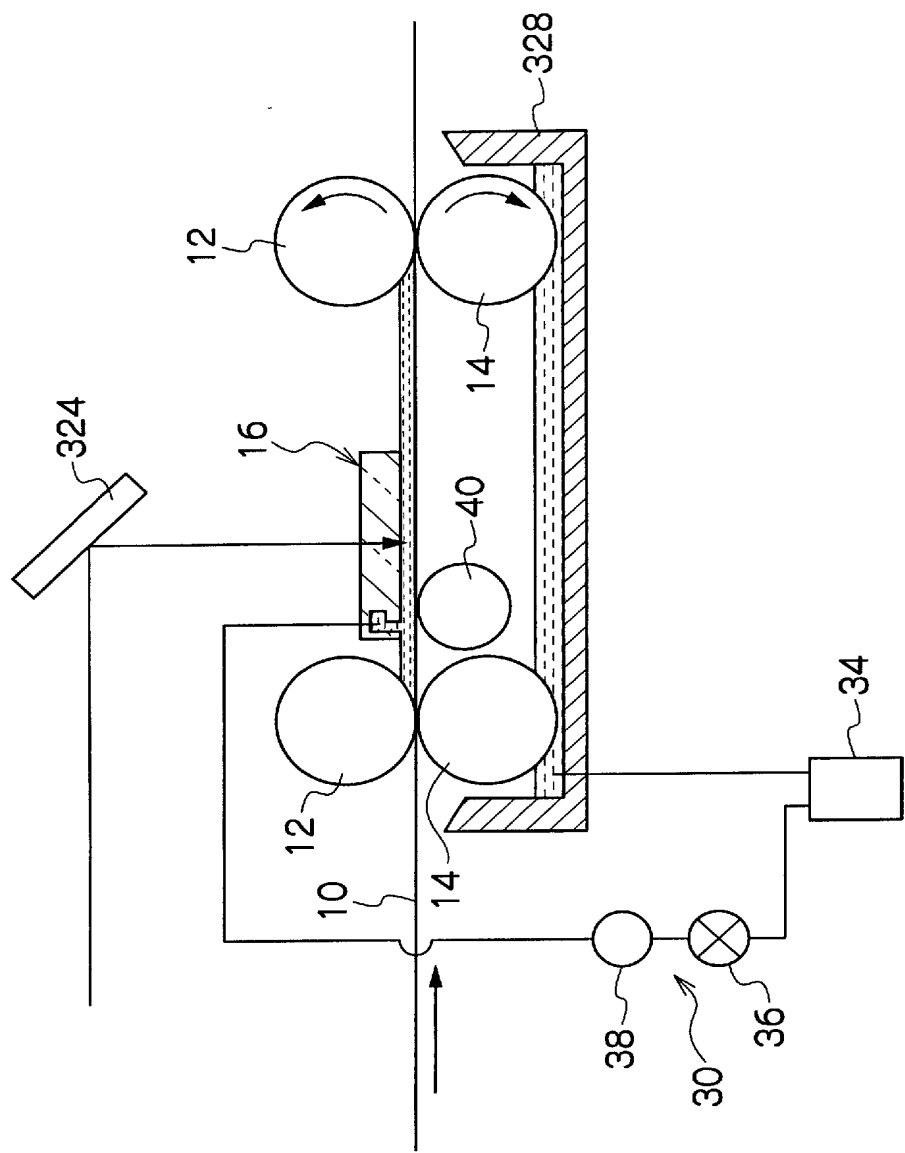
[図7]



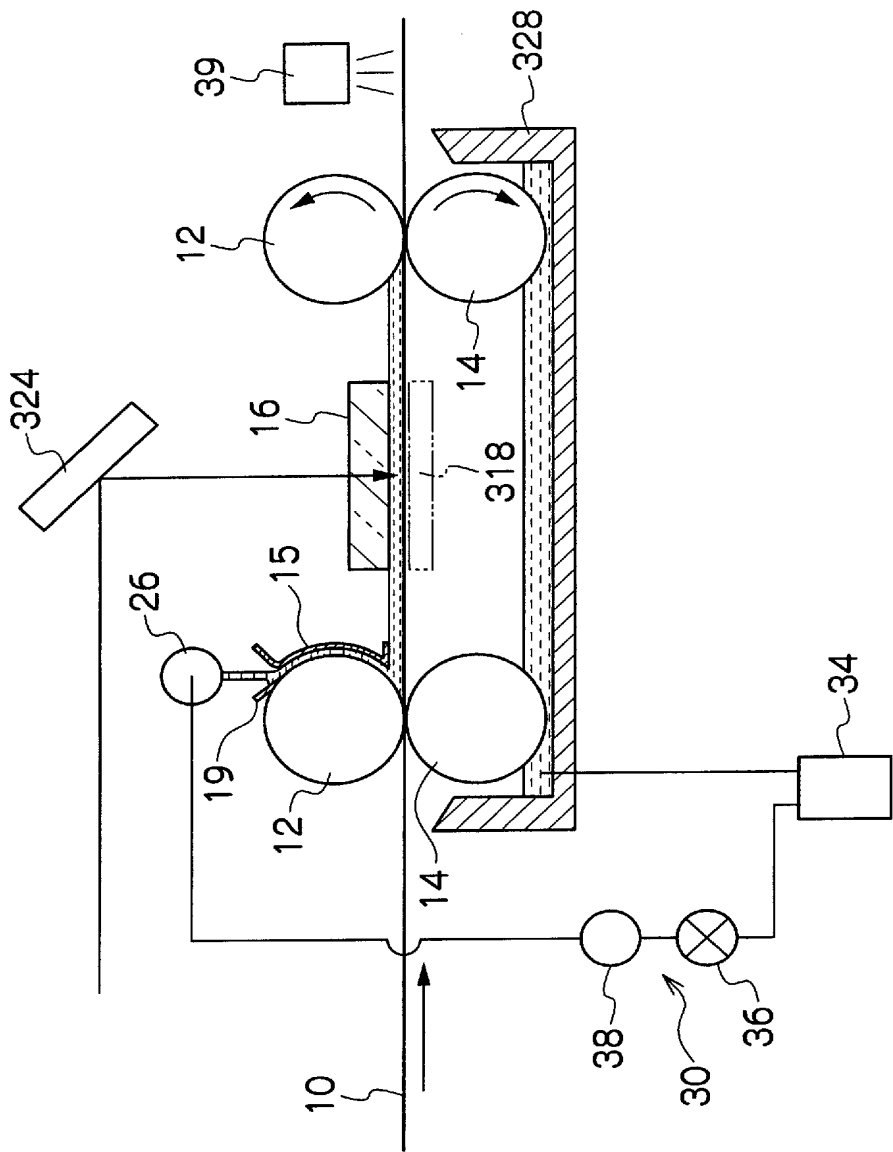
[图8]



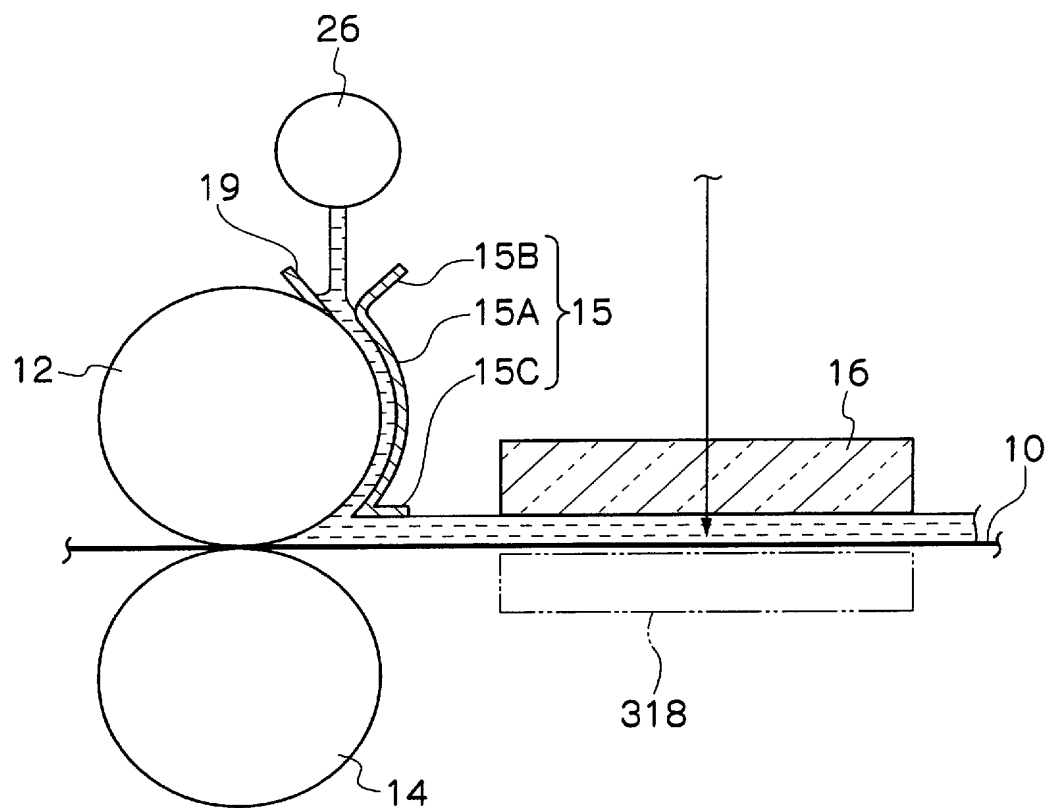
[図9]



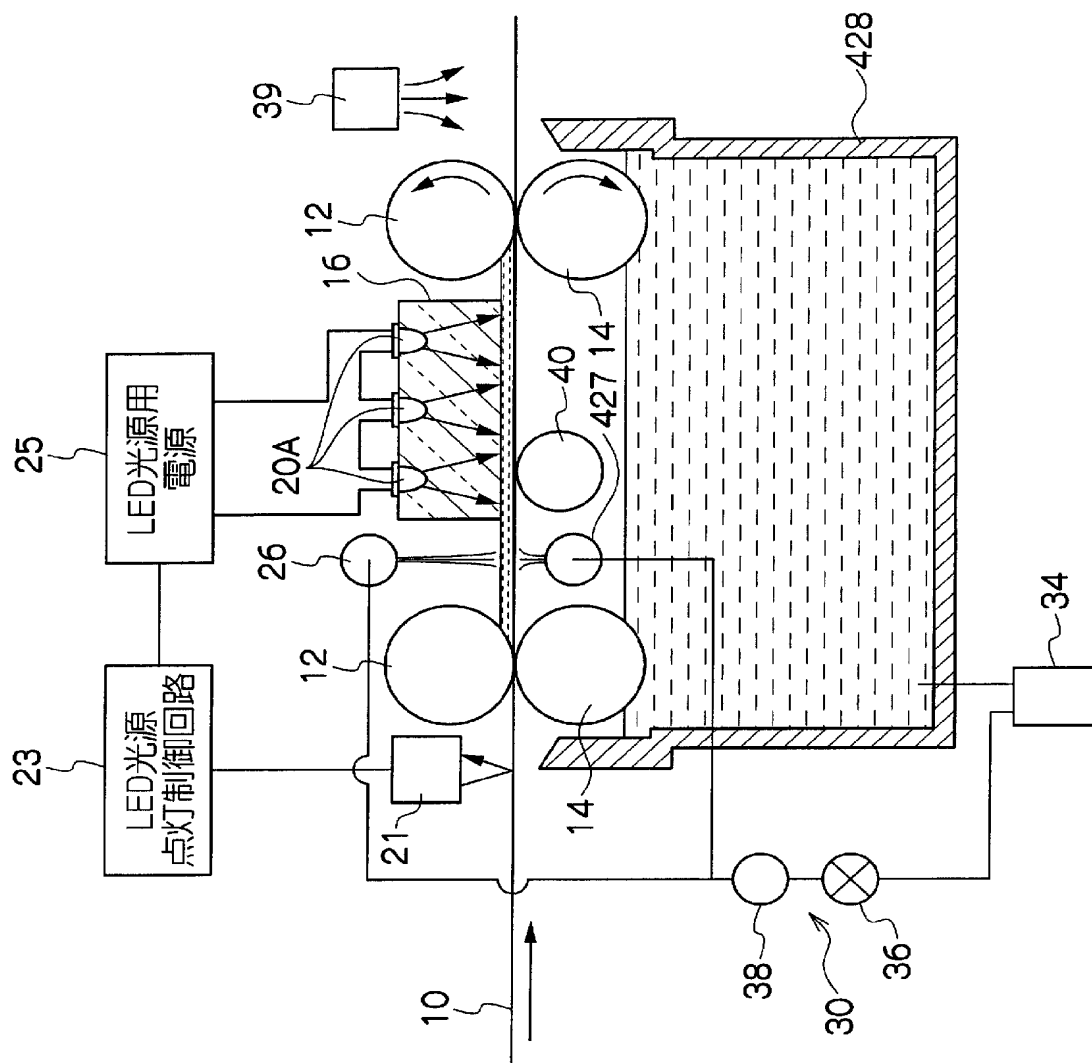
[図10]



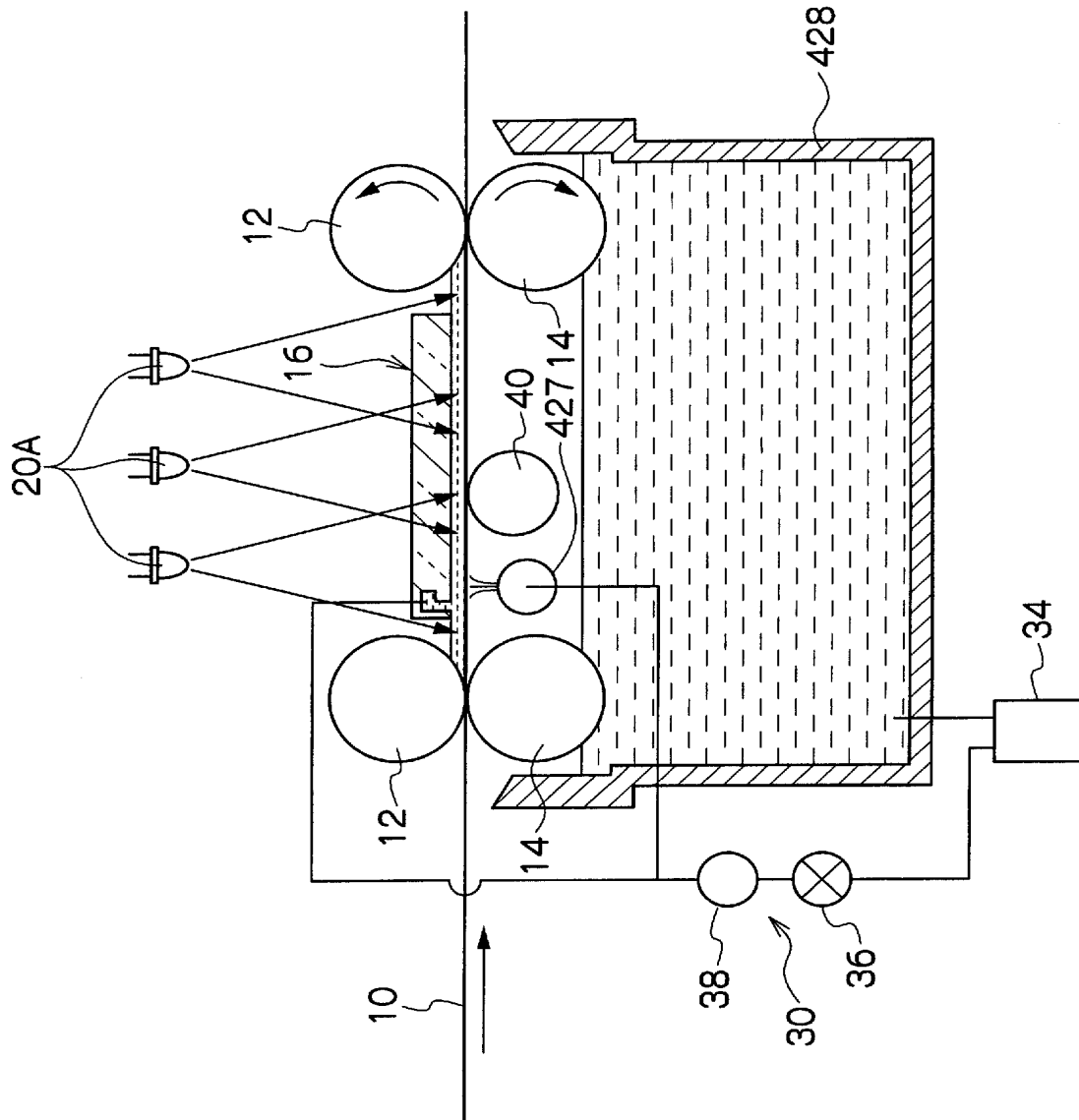
[図11]



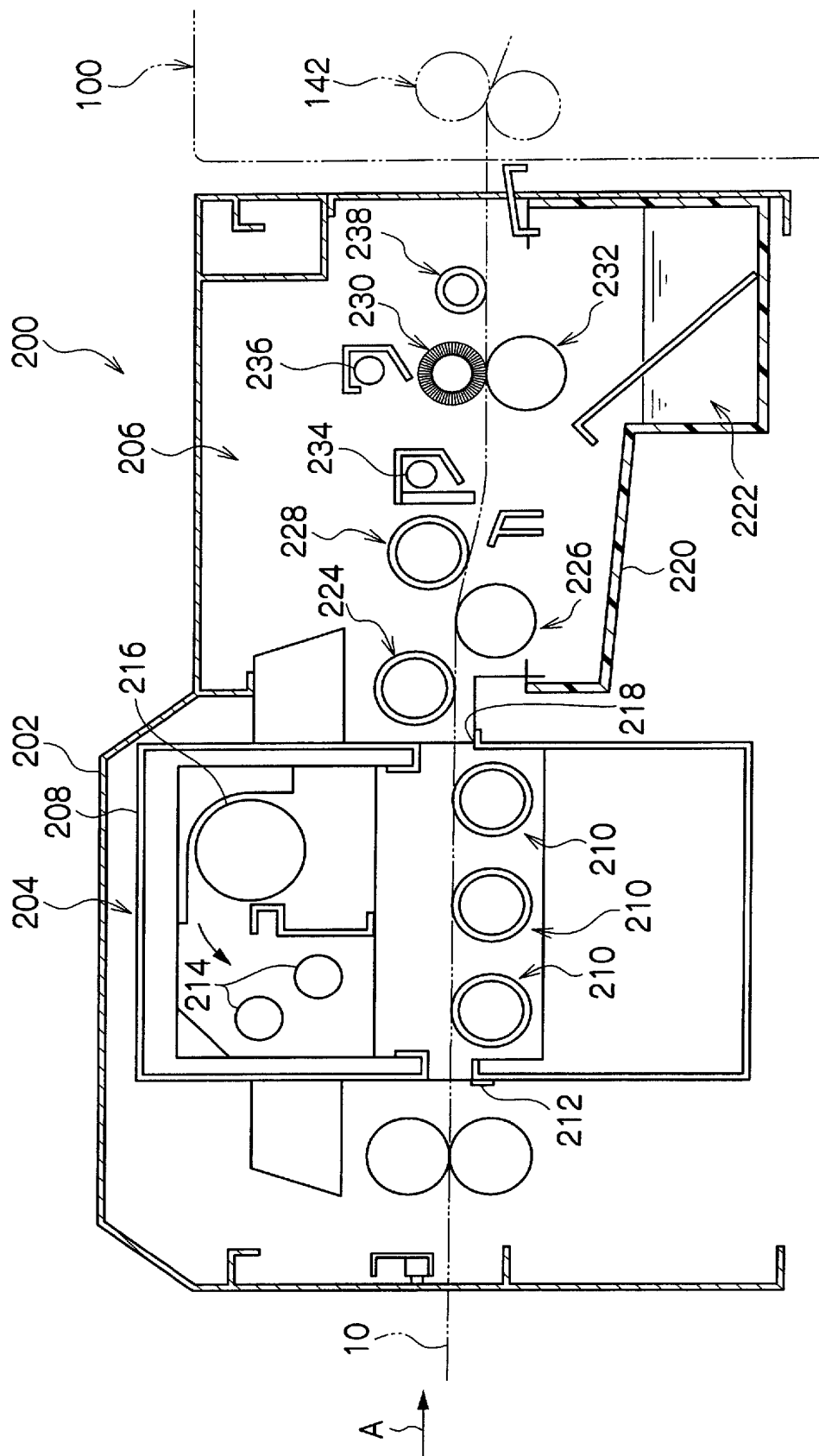
[図13]



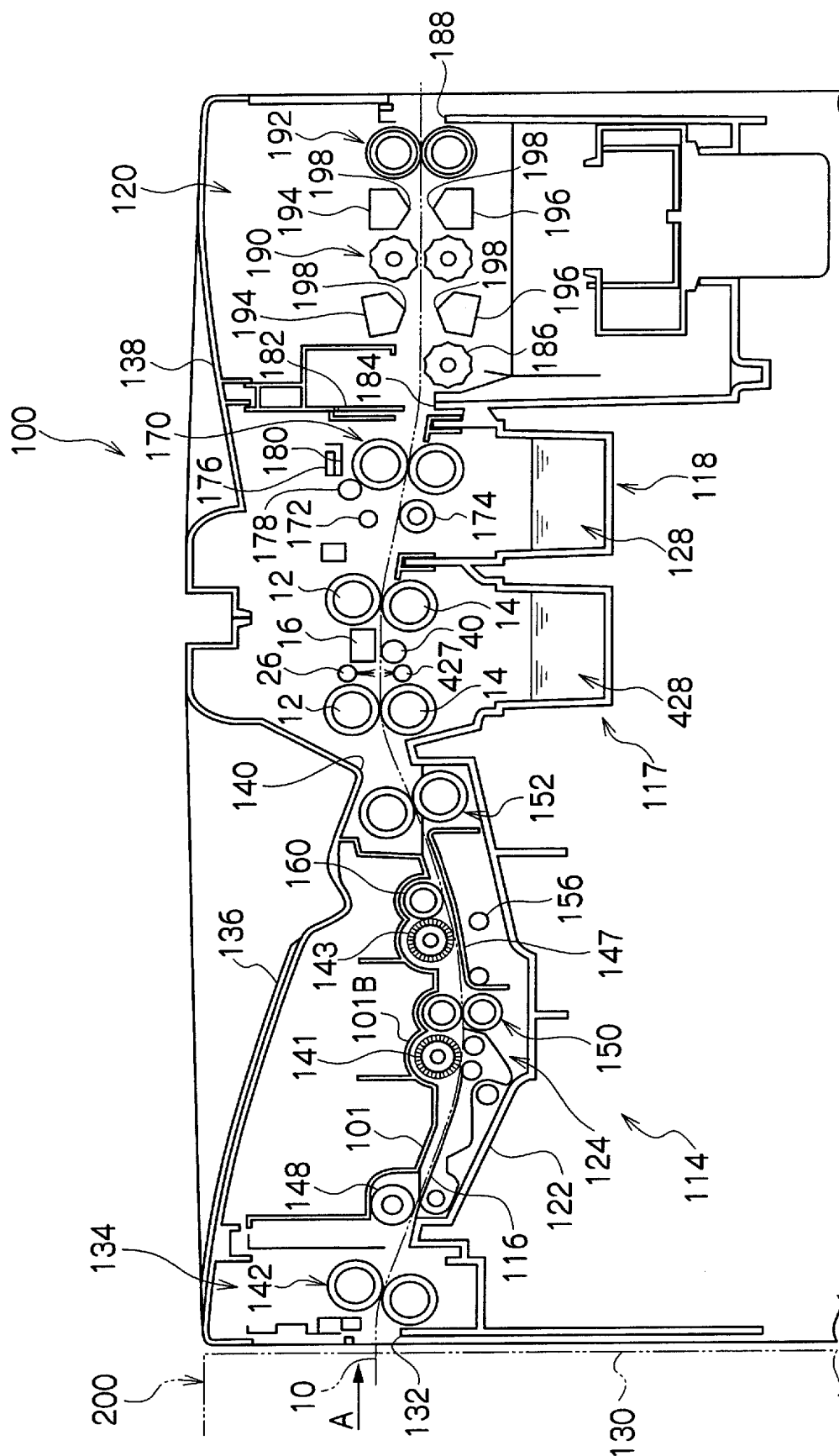
[図14]



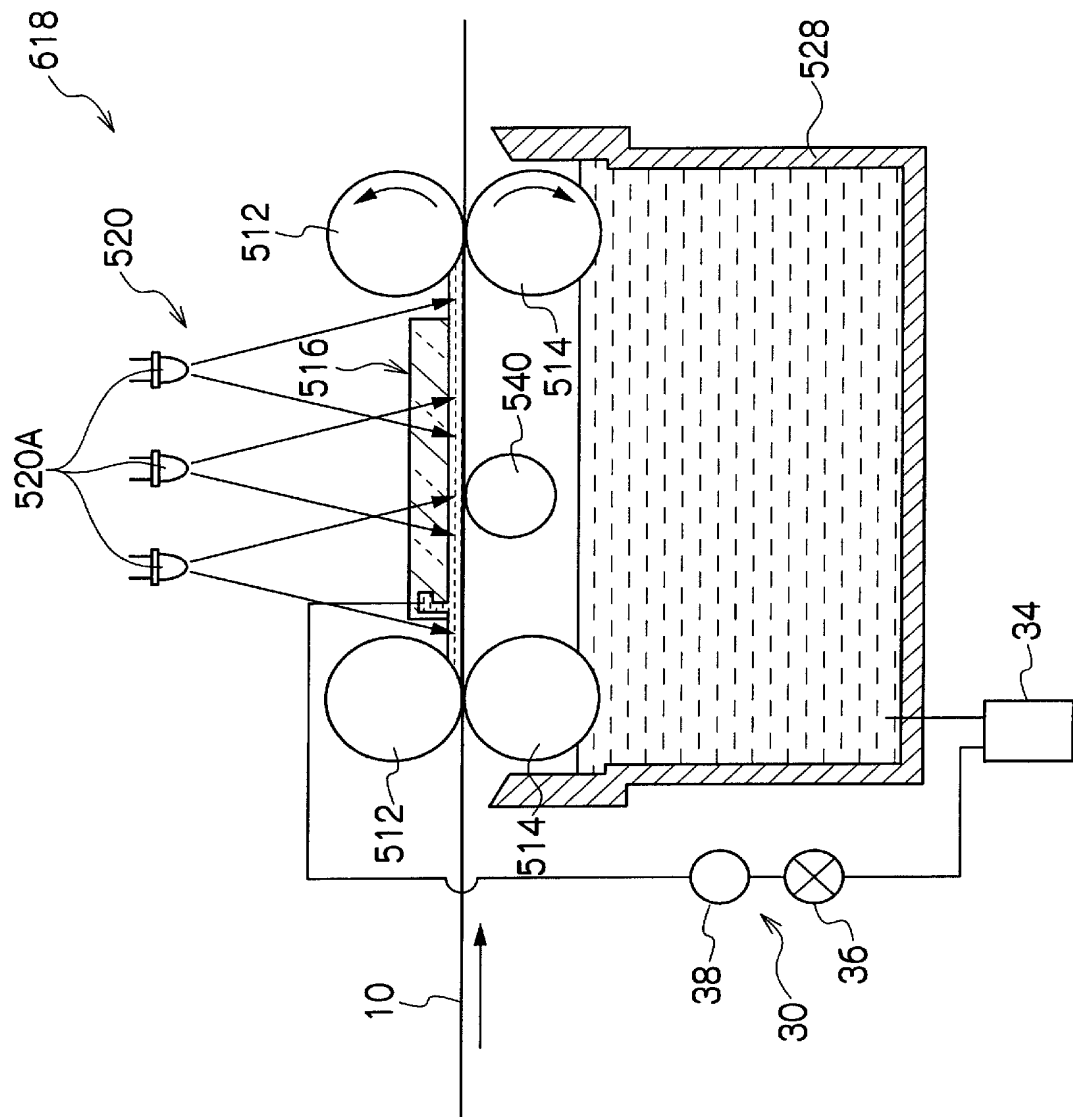
[図16]



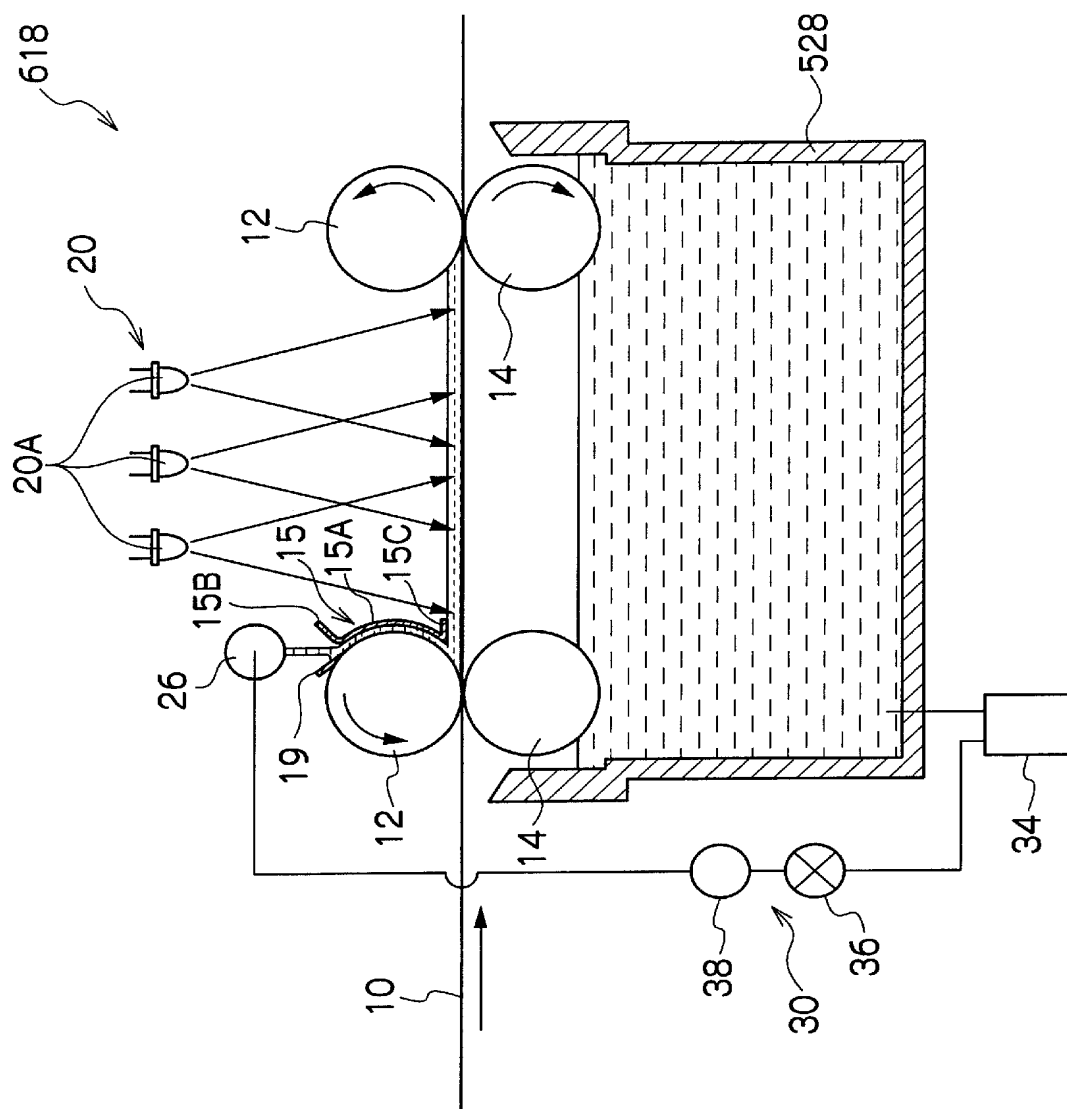
[図17]



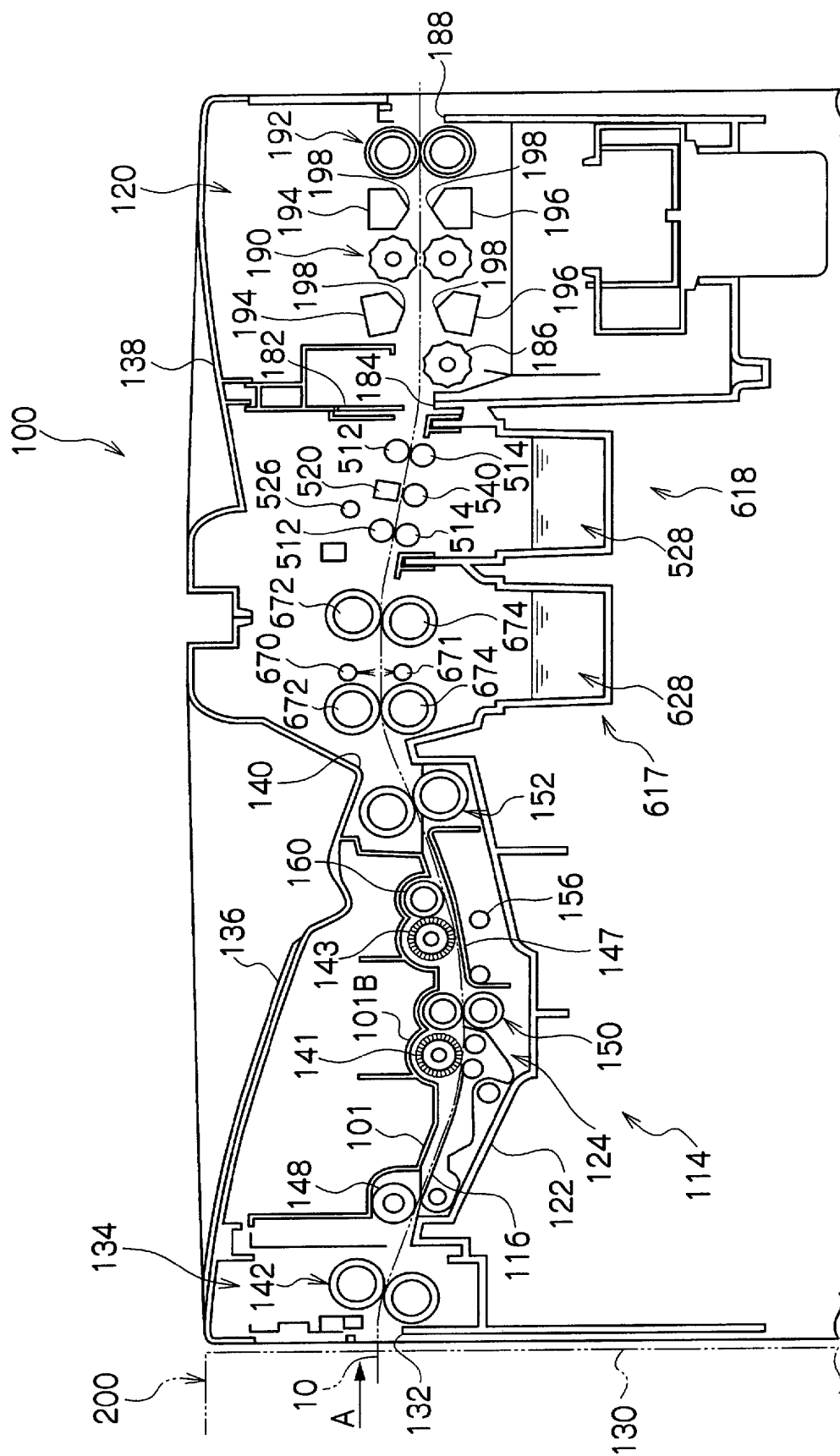
[図20]



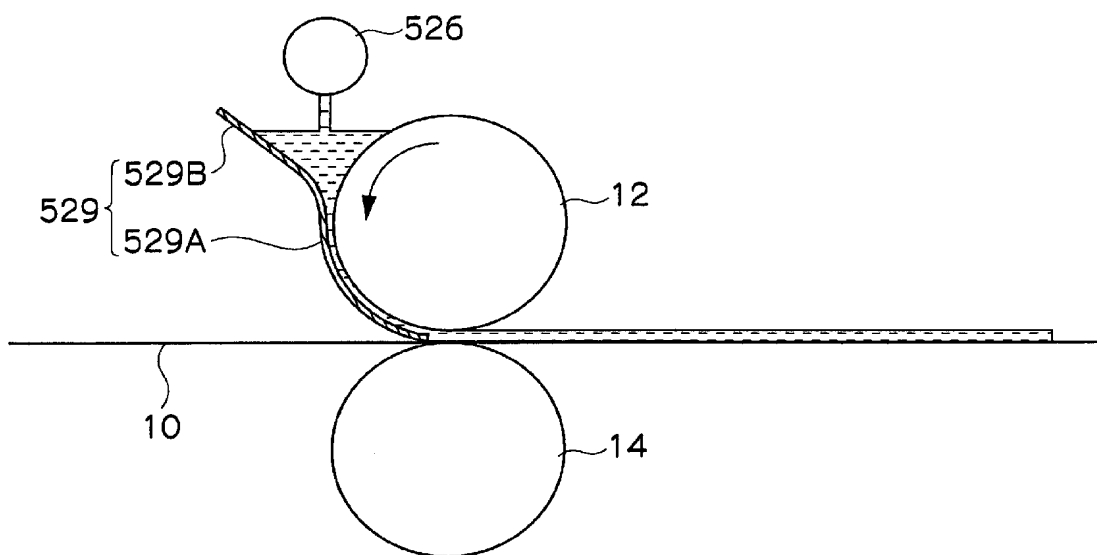
[図21]



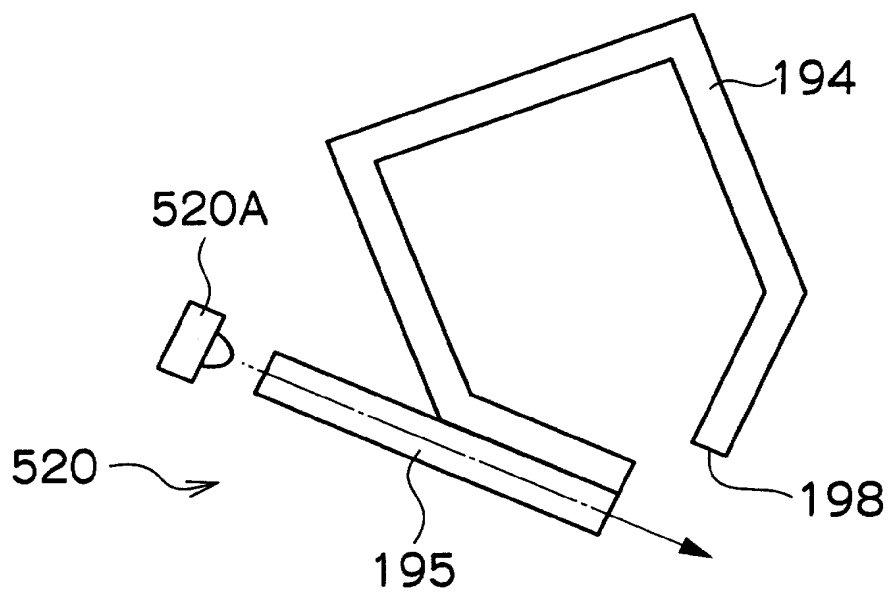
[図22]



[図23]



[図24]



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2006/323192

A. CLASSIFICATION OF SUBJECT MATTER

G03F7/30(2006.01)i, G03F7/00(2006.01)i, G03F7/20(2006.01)i, G03F7/40(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G03F7/30, G03F7/00, G03F7/20, G03F7/40

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2007
Kokai Jitsuyo Shinan Koho 1971-2007 Toroku Jitsuyo Shinan Koho 1994-2007

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP 50-95001 A (Asahi Chemical Industry Co., Ltd.), 29 July, 1975 (29.07.75), Full text (Family: none)	1, 14 2-13, 15-19
X Y	WO 86/2177 A1 (MACDERMID, INC.), 10 April, 1986 (10.04.86), Full text & US 4603058 A1 & JP 62-500404 A	1, 14 2-13, 15-19
X Y	JP 2004-341286 A (Asahi Kasei Chemicals Corp.), 02 December, 2004 (02.12.04), Claims; Par. Nos. [0029] to [0041], [0106] (Family: none)	1, 14 2-13, 15-19

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
19 February, 2007 (19.02.07)

Date of mailing of the international search report
27 February, 2007 (27.02.07)

Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2006/323192

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP 2005-84418 A (Asahi Kasei Chemicals Corp.), 31 March, 2005 (31.03.05), Full text (Family: none)	1, 14 2-13, 15-19
X Y	JP 54-12904 A (Fuji Photo Film Co., Ltd.), 31 January, 1979 (31.01.79), Full text & US 4258122 A1	1, 14, 17 2-13, 15, 16, 18, 19
X Y	JP 2004-61695 A (Mitsubishi Chemical Corp.), 26 February, 2004 (26.02.04), Full text (Family: none)	1, 14, 17 2-13, 15, 16, 18, 19
Y	JP 2002-162753 A (Mitsubishi Chemical Corp.), 07 June, 2002 (07.06.02), Full text; all drawings (Family: none)	1-19
Y	JP 2001-159811 A (Fuji Photo Film Co., Ltd.), 12 June, 2001 (12.06.01), Full text; all drawings (Family: none)	1-19
Y	JP 2001-51426 A (Fuji Photo Film Co., Ltd.), 23 February, 2001 (23.02.01), Full text; all drawings (Family: none)	1-19
Y	JP 2001-48326 A (Fuji Photo Film Co., Ltd.), 20 February, 2001 (20.02.01), Full text; all drawings (Family: none)	1-19

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int.Cl. G03F7/30(2006.01)i, G03F7/00(2006.01)i, G03F7/20(2006.01)i, G03F7/40(2006.01)i

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int.Cl. G03F7/30, G03F7/00, G03F7/20, G03F7/40

最小限資料以外の資料で調査を行った分野に含まれるもの

日本国実用新案公報	1922-1996年
日本国公開実用新案公報	1971-2007年
日本国実用新案登録公報	1996-2007年
日本国登録実用新案公報	1994-2007年

国際調査で使用した電子データベース (データベースの名称、調査に使用した用語)

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X Y	J P 50-95001 A (旭化成工業株式会社) 1975.07.29、全文、(ファミリーなし)	1, 14 2-13, 15-19
X Y	WO 86/2177 A1 (MACDERMID, INCORP ORATED) 1986.04.10、全文 & US 460 3058 A1 & J P 62-500404 A	1, 14 2-13, 15-19
X Y	J P 2004-341286 A (旭化成ケミカルズ株式会社) 2004.12.02、[特許請求の範囲]、[0029] - [004	1, 14 2-13, 15-19

☒ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願

の日の後に公表された文献

「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日

19.02.2007

国際調査報告の発送日

27.02.2007

国際調査機関の名称及びあて先

日本国特許庁 (ISA/J P)
郵便番号100-8915
東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

前田 佳与子

2H

9019

電話番号 03-3581-1101 内線 3231

C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
	1], [0 1 0 6] (ファミリーなし)	
X	J P 2 0 0 5 - 8 4 4 1 8 A (旭化成ケミカルズ株式会社)	1, 14
Y	2 0 0 5 . 0 3 . 3 1、全文 (ファミリーなし)	2-13, 15-19
X	J P 5 4 - 1 2 9 0 4 A (富士写真フイルム株式会社)	1, 14, 17
Y	1 9 7 9 . 0 1 . 3 1、全文 & U S 4 2 5 8 1 2 2 A 1	2-13, 15, 16, 18, 19
X	J P 2 0 0 4 - 6 1 6 9 5 A (三菱化学株式会社)	1, 14, 17
Y	2 0 0 4 . 0 2 . 2 6、全文 (ファミリーなし)	2-13, 15, 16, 18, 19
Y	J P 2 0 0 2 - 1 6 2 7 5 3 A (三菱化学株式会社)	1-19
	2 0 0 2 . 0 6 . 0 7、全文全図 (ファミリーなし)	
Y	J P 2 0 0 1 - 1 5 9 8 1 1 A (富士写真フイルム株式会社)	1-19
	2 0 0 1 . 0 6 . 1 2、全文全図 (ファミリーなし)	
Y	J P 2 0 0 1 - 5 1 4 2 6 A (富士写真フイルム株式会社)	1-19
	2 0 0 1 . 0 2 . 2 3、全文全図 (ファミリーなし)	
Y	J P 2 0 0 1 - 4 8 3 2 6 A (富士写真フイルム株式会社)	1-19
	2 0 0 1 . 0 2 . 2 0、全文全図 (ファミリーなし)	

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International Bureau



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C07D 471/04 (2006.01) **A61K 31/52** (2006.01)

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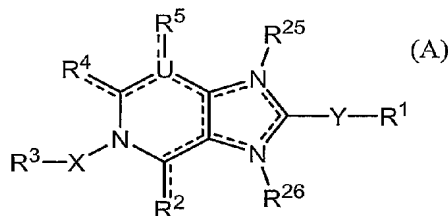
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(54) Title: IMIDAZO[4,5-D]PYRIMIDINES, THEIR USES AND METHODS OF PREPARATION



(57) Abstract: The present invention relates to pharmaceutical compositions for the treatment of prevention of viral infections comprising as an active principle at least one imidazo[4,5-c]pyrimidine having the general formula (A), wherein the substituents are described in the specification. The invention also relates to processes for the preparation of compounds according to the invention having above mentioned general formula, their pharmaceutically acceptable formulations and their use as a medicine or to treat or prevent viral infections.



WO 2006/033703 A1

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10 **Imidazo[4,5-d]pyrimidines, Their Uses and Methods of Preparation**

15 **FIELD OF THE INVENTION**

15

The present invention relates to imidazo[4,5-d]pyrimidines, their uses and manufacture. The invention relates specifically to antiviral compounds, in particular such compounds for the treatment of Flaviviridae and Picornaviridae.

20 **BACKGROUND OF THE INVENTION**

The family of the Flaviviridae consists of 3 genera, the pestiviruses, the flaviviruses and the hepaciviruses and also contains the hepatitis G virus (HGV/GBV-C) that has not yet been assigned to a genus. Pestiviruses such as the
25 Classical Swine Fever Virus (CSFV), the Bovine Viral Diarrhea Virus (BVDV) and the Border Disease Virus (BDV) cause infections of domestic livestock (respectively pigs, cattle and sheep) and are responsible for significant economic losses world-wide. BVDV, the prototypic representative of the pestivirus genus is
30 ubiquitous and causes a range of clinical manifestations, including abortion, teratogenesis, respiratory problems, chronic wasting disease, immune system dysfunction, and predisposition to secondary viral and bacterial infections and

may also cause acute fatal disease. Fetuses of cattle can be infected persistently with BVDV, these animals remain viremic throughout life and serve as a continuous sources for virus spread in herds.

Vaccines are used in some countries with varying degrees of success to control pestivirus disease. In other countries, animal culling and slaughter are used to contain pestivirus disease outbreaks.

The World Health Organization estimates that world-wide 170 million people (3% of the world's population) are chronically infected with HCV (Hepatitis C Virus). These chronic carriers are at risk of developing cirrhosis and/or liver cancer. In studies with a 10 to 20 year follow-up, cirrhosis developed in 20 – 30% of the patients, 1 to 5% of whom may develop liver cancer during the next ten years. The only treatment option available today is the use of interferon α -2 (or its pegylated form) either alone or combined with ribavirin. However, sustained response is only observed in about 40% of the patients and treatment is associated with serious adverse effects. There is thus an urgent need for potent and selective inhibitors of the replication of HCV in order to treat infections with HCV. Furthermore, the study of specific inhibitors of HCV replication has been hampered by the fact that it is not possible to propagate HCV (efficiently) in cell culture. Since HCV and pestiviruses belong to the same virus family and share many similarities (organization of the genome, analogous gene products and replication cycle), pestiviruses have been adopted as a model and surrogate for HCV. For example BVDV is closely related to hepatitis C virus (HCV) and used as a surrogate virus in drug development for HCV infection.

The compound 3-(((2-dipropylamino)ethyl)thio)-5H-1,2,4-triazino[5,6-b]indole has been reported to selectively inhibit the replication of BVDV and other pestiviruses (Baginski SG et. al., Proc. Natl. Acad. Sci. U.S.A. 2000 Jul 5;97(14):7981-6). Currently, there is no antiviral treatment for pestiviral infections.

Coxsackie viruses belong to the group of the enteroviruses, family of the Picornaviridae. They cause a heterogeneous group of infections including herpangina, aseptic meningitis, a common-cold-like syndrome, a non-paralytic

poliomyelitis-like syndrome, epidemic pleurodynia (an acute, febrile, infectious disease generally occurring in epidemics), hand-foot-mouth syndrome, pediatric and adult pancreatitis and serious myocarditis.

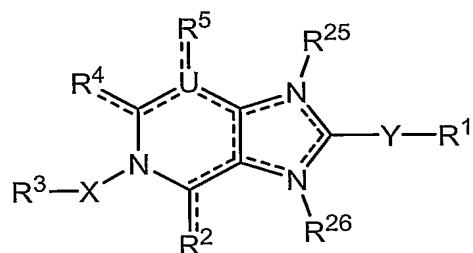
Currently only pleconaril (3-13,5-dimethyl-4-[[3-methyl-5-isoxazolyl)propyl]phenyl]-5-(trifluoromethyl-1,2,4-oxadiazole)) and enviroxime (2-amino-1-(isopropylsulfonyl)-6-benzimidazole phenyl ketone oxime) have been studied clinically for the treatment of infections with enteroviruses. Pleconaril is a so called "capsid function-inhibitor"; enviroxime prevents the formation of the RNA replicative intermediate. Enviroxime resulted in only modest clinical and virological benefit in some studies and no benefits in others. Clinical response with Pleconaril has been observed in some studies, but the compound has not been marketed.

Reference is made to U.S. Patent Nos. 4,914,108, 4,990,518, 4,988,707, 5,227,384, 5,302,601 and 5,486,525, EP 113238, WO 96/1192, WO 96/12703, Chemical Abstracts acc no. 1987:18435 and Chemical Abstracts acc no. 1983:594812, EP 1162196, WO 95/02597, WO 04/033455; WO 2004/018468; WO 03/014229; WO 02/067942; WO 00/073307 and US 2004/0122228.

A need exists for compounds having activity against the Picornaviridae and Flaviviridae, in particular HCV, having improved physicochemical and/or pharmacological properties.

SUMMARY OF THE INVENTION

The compounds of this invention have the general formula (A),



(A)

wherein:

the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

U is N;

R¹ is selected from aryl, heterocycle, C₁-C₁₀ alkoxy, C₁-C₁₀ thioalkyl, C₁-C₁₀ alkyl-amino, C₁-C₁₀ dialkyl-amino, C₃₋₁₀ cycloalkyl, C₄₋₁₀ cycloalkenyl, and C₄₋₁₀ cycloalkynyl, wherein each are optionally substituted with 1 or more R⁶;

Y is selected from a single bond, O, S(O)_m (where m is an integer from 0 to 2), NR¹¹, C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, and C₂₋₁₀ alkynylene, or C₁₋₁₀ alkylene, C₂₋₂₀ alkenylene or C₂₋₁₀ alkynylene, wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR¹¹;

R² and R⁴ are independently selected from hydrogen, C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, C₂₋₁₈ alkynyl, C₁₋₁₈ alkoxy, C₁₋₁₈ alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸, haloalkyloxy, haloalkyl, -C(=O)R⁹, -C(=S)R⁹, SH, aryl, aryloxy, arylthio, arylalkyl, C₁₋₁₈ hydroxyalkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, C₃₋₁₀ cycloalkylthio, C₃₋₁₀ cycloalkenyl, C₇₋₁₀ cycloalkynyl, and heterocycle, provided that when one of R²⁵ or R²⁶ is present, then either R² or R⁴ is selected from =O, =S, or =NR²⁷;

X is selected from C₁-C₁₀ alkylene, C₂₋₁₀ alkenylene or C₂₋₁₀ alkynylene, where each may include one or more heteroatoms selected from O, S, or NR¹¹, provided any such heteroatom is not adjacent to the N in the ring;

R³ is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R¹⁰)-, or heterocycle, where each said substituent is optionally substituted with at least one R¹⁷, provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R⁵ independently is absent or is selected from hydrogen, C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, C₂₋₁₈ alkynyl, C₁₋₁₈ alkoxy, C₁₋₁₈ alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸,

haloalkyloxy, haloalkyl, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=S)R^9$, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, and heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl, $-C(O)OR^{18}$, NO_2 , $-NR^7R^8$, C_{1-18} haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, and C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19} ;

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, $-C(=O)R^{12}$, $-C(=S)R^{12}$, an amino acid residue linked through a carboxyl group thereof, and the group formed when R^7 and R^8 are taken together with the nitrogen to form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, $-NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1 - C_{12} alkyl, C_6 - C_{20} aryl, C_6 - C_{20} alkylaryl or C_6 - C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, and an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, arylalkyl (unsubstituted or substituted with $C(O)OR^{18}$), C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{17} is independently selected from the group consisting of (a) hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halogenated alkyl, C_{2-18} halogenated alkenyl, C_{2-18} halogenated alkynyl, C_{1-18} halogenated alkoxy, C_{1-18} halogenated alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, CO_2H , CO_2R^{18} , NO_2 , NR^7R^8 , haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle, and C_{1-18} hydroxyalkyl, where each of said aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle, or C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} , and (b) M-Q- wherein M is a ring optionally substituted with 1 or more R^{19} , and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R^{19} ;

R^{19} is selected from

- (a) H;
- (b) NO_2 , SH, $NR^{20}R^{21}$, OH, halogen and CN;
- (c) Sulfone, sulfonamide and sulfoxide;
- (d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;
- (e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20} , $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;
- (f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;
- (g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}=O$, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;
- (h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle, and heterocycle substituted with C_1 - C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

5 (k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl,
10 $-C(=O)R^{12}$, and $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl, heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , benzyloxy, and OH;

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, $(C_{3-10}$ cycloalkyl)- C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl; and
15 salts, tautomers, polymorphs, isomers and solvates thereof.

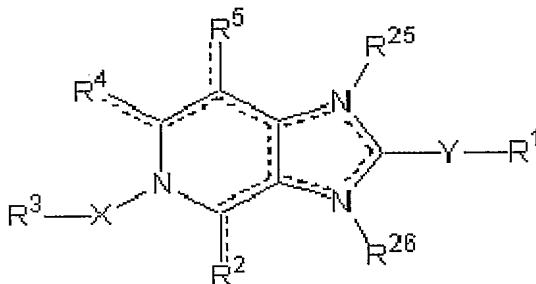
In a further embodiment of the invention the compounds of the formulas of this invention are optionally combined with pharmacologically acceptable
20 excipients.

In a further embodiment of the invention the compounds of the formulas of this invention are administered in therapeutically effective amounts to subjects (humans or animals) in need of antiviral therapy, in particular for inhibiting the infection, growth or replication of Flaviviridae and Picornaviridae, especially
25 BVDV, HCV and Coxsackie virus.

The invention further relates to a method of screening antiviral compounds which comprises providing a compound of formula (A) and determining the antiviral activity of said compound.

Also within the scope of the invention is a metabolite of the compounds of the formulas of this invention made by the process of administering a compound of formula (A) to a subject and recovering the metabolite from the subject.

The invention also comprises a method for structure-activity determination
5 of analogues of compounds of WO 04/005286 having the general structure



wherein

the R, X and Y groups are defined in WO 04/005286, comprising

- (A) preparing an analogue of a compound falling within the scope of
10 WO 2004/005286 wherein C₇ is replaced by N; and
- (B) determining the anti-HCV activity of the compound of step (A).

Detailed Description of the Invention

15 Definitions

"Alkyl" means saturated hydrocarbon moiety where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain 1 to 3 carbon atoms, and each ring may contain 3 to 6 carbon atoms
20 (for example, 3-methylcyclohexyl). Within this definition, the term "cycloalkyl" refers to the saturated hydrocarbon moieties that are cyclic. Examples of "alkyl" include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl(i-Bu), 2-butyl (s-Bu) 2-methyl-2-propyl (t-Bu), 1-pentyl (n-pentyl), 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl,
25 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cyclopropyl, cyclobutyl,

cyclopentyl, cycloheptyl, cyclooctyl and the like, or a C₇₋₁₀ polycyclic saturated hydrocarbon radical having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl.

“Alkenyl” means a hydrocarbon moiety with at least one site of double bond unsaturation where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain 1 to 3 carbon atoms, and each cyclic portion may contain 3 to 6 carbon atoms. A site of double bond unsaturation may be in a acyclic portion, a cyclic portion. In the instance of a moiety having a combination of acyclic and cyclic portions, there may be a site of double bond unsaturation in each of the portions. Within this definition, the term “cycloalkenyl” refers to the double bond unsaturated hydrocarbon moieties that are cyclic. Examples the term “alkenyl” include, but are not limited to, ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂), 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, and 1-cyclohex-3-enyl. The double bond optionally is in the cis or trans configuration.

“Alkynyl” means a hydrocarbon moiety with a least one site of triple bond unsaturation where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain contain 1 to 3 carbon atoms, and each cyclic portion may contain 7 or more carbon atoms. Within this definition, the term “cycloalkynyl” refers to triple bond unsaturated hydrocarbon moieties that are cyclic. Examples of the term “alkynyl” include, but are not limited to, -CCH, -CH₂CCH, -CH₂CC-cyclohexyl, or -CH₂-cycloheptynyl.

The suffix “-ene” used in connection with alkyl, alkenyl and alkynyl groups refers to such groups with at least 2 sites of substitution. Such polyvalent hydrocarbon radicals include, but are not limited to, methylene (-CH₂-) 1,2-ethylene (-CH₂CH₂-), 1,3-propylene (-CH₂CH₂CH₂-), 1,4-butylene (-CH₂CH₂CH₂CH₂-), 1,2-ethylene (-CH=CH-), -CC-, propargyl (-CH₂CC-), and 4-pentynyl (-CH₂CH₂CH₂CCH-). Optionally, alkylene, alkenylene and alkynylene are substituted with O, S or N, generally meaning that O, S or N replace a carbon

atom and the valence appropriate number of carbon substituents (generally 1 or 2H). N in this case is generally R¹¹.

"Aryl" means an aromatic hydrocarbon containing 1 or more rings, generally 1, 2 or 3, with 4 to 6 carbon atoms in each, ordinarily 5 or 6 carbon
5 atoms.

"Arylalkyl," "arylalkenyl" and "arylalkynyl" means an alkyl, alkenyl or alkynyl radical, respectively, in which one of the hydrogen atoms, typically a terminal or sp³ carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-
10 1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like.

As noted, carbocycles optionally are found as single rings or multiple ring systems. Ordinarily the hydrocarbons of the compounds of the formulas of this invention are single rings. Monocyclic carbocycles generally have 3 to 6 ring
15 atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system.

If the number of carbon atoms is unspecified for a hydrocarbon, typically the number of carbon atoms will range from 1 to 18, except that the number of
20 carbons typically will range from 2 to 18 for unsaturated hydrocarbons and from 6 to 10 for aryl.

"Heterocycle" or "heterocycle" means any 4, 5, 6, 7, 8 or 9 membered single or fused ring system containing one or more heteroatoms selected from the group consisting of O, N or S. Heterocycles optionally are entirely aromatic, entirely
25 saturated, or contain 1 or more intra-ring sites of unsaturation, typically double bonds. Multiple heterocyclic rings (one or more of which contains a heteroatom) are bridged or spiro. Generally, the heterocyclic rings will be aromatic, and usually they are single rings. Examples of heterocycles include oxazacycloalkyl, morpholinyl, dioxacycloalkyl, thiacycloalkenyl, pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, furanyl, thienyl,
30

pyrrolyl, pyranlyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, piperazinyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-
5 tetrahydropyranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thianthrenyl, pyranlyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isothiazoledinyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolidinyl,
10 pyrrolinyl, indoliziny, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl,
15 imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolyl, isoindolyl, quinuclidinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolyl, benzothienyl, benzothiazolyl and isatinoyl. Other suitable heterocycles are exemplified in Rigaudy et. al., Nomenclature of Organic Chemistry, Sections A-H (1979) at pp. 53-76 and Fletcher et. al., Nomenclature of
20 Organic Compounds, Adv. Chem. Ser. 126 (1974) at pp 49-64.

The location on the heterocycle which provides the point of attachment(s) to the rest of the compound of this invention is not critical, but those skilled in the art will recognize substitution sites that are optimal for compound stability and/or ease of synthesis. Carbon bonded heterocycles typically are bonded at
25 position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or
30 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include

2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

5 Nitrogen containing heterocycles are bonded at nitrogen or a carbon, typically a carbon atom. These include, for example, position 1 of aziridine, 1-aziridyl, 1-azetedy, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, 1-piperidinyl, 2-pyrroline, 3-pyrroline, 2-imidazoline, 3-imidazoline, 9-carbazole, 4-morpholine, 9-alpha or β -carboline, 2-isoindole, 2-pyrazoline and 3-pyrazoline, and by analogy, 10 azetidine, pyrrole, pyrrolidine piperidine, piperazine, indole, pyrazoline, indoline, imidazole, imidazolidine, 1H-indazole and isoindoline. These and other N-containing heterocycles are well-known to those skilled in the art, and their linkage sites are a matter of discretion.

Sulfur containing heterocycles are bonded through carbon or sulfur. They 15 include oxidized states such as $-S(=O)(=O)$. In general, they are linked in the compounds of the formulas of this invention analogous to N-containing heterocycles.

"Alkoxy", "cycloalkoxy", "aryloxy", "arylalkyloxy", "oxy heterocycle", "thioalkyl", "thiocycloalkyl", "arylthio", and "arylalkylthio" means substituents 20 wherein an alkyl, cycloalkyl, aryl, or arylalkyl, respectively, are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzyloxy, mercaptobenzyl and the like.

"Halogen" means any atom selected from the group consisting of fluorine, 25 chlorine, bromine and iodine.

Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

When a group is stated to be substituted with "one or more" of another group, this typically means 1 to 3 substituents, ordinarily 1, 2 or 3 substituents.

30 Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among

other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state--any and all
5 protonated forms of the compounds are intended to fall within the scope of the invention.

Amino Acids

10 "Amino-acid" refers to a radical derived from a molecule having the chemical formula $H_2N-CHR^{28}-COOH$, wherein R^{28} is a side group of a naturally-occurring or known synthetic amino-acid. The amino acids optionally are substituted with hydrocarbon typically of 1 to 8 carbons at one or more carboxyl or amino groups, whether those groups are on the side chain or are free after
15 linking the amino acid to the remainder of the compound of this invention.

Optionally the amino acid residue is a hydrophobic residue such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. Optionally, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally
20 in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline,
25 asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included.

Generally, only one of any site in the parental molecule is substituted with an amino acid, although it is within the scope of this invention to introduce amino acids at more than one permitted site. In general, the alpha-amino or alpha-
30 carboxyl group of the amino acid are bonded to the remainder of the molecule, i.e., carboxyl or amino groups in the amino acid side chains generally are not used

to form amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates).

The amino acid esters optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Optionally, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments.

R²⁸ usually is C₁-C₆ alkyl or C₁-C₆ alkyl substituted with amino, carboxyl, amide, carboxyl (as well as esters, as noted above), hydroxyl, C₆-C₇ aryl, guanidiny, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R²⁸ also is taken together with the amino acid alpha nitrogen to form a proline residue. However, R²⁸ is generally the side group of the naturally-occurring amino acid disclosed above, for example H, -CH₃, -CH(CH₃)₂, -CH₂-CH(CH₃)₂, -CHCH₃-CH₂-CH₃, -CH₂-C₆H₅, -CH₂CH₂-S-CH₃, -CH₂OH, -CH(OH)-CH₃, -CH₂-SH, -CH₂-C₆H₄OH, -CH₂-CO-NH₂, -CH₂-CH₂-CO-NH₂, -CH₂-COOH, -CH₂-CH₂-COOH, - (CH₂)₄-NH₂ and -(CH₂)₃-NH-C(NH₂)-NH₂. R²⁸ also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Subgeneric Embodiments

R¹ is generally aryl or aromatic heterocycle (usually containing 1 or 2 O, S or N atoms, typically O or S) substituted with 1, 2 or 3 R⁶ wherein R⁶ usually is halogen, C₁₋₁₈ alkoxy; or C₁₋₁₈ haloalkyl. Typically, R¹ is 6 to 10 C carbocycle having 1 or 2 rings (most ordinarily phenyl) substituted with 1, 2 or 3 halogens, usually fluoro.

Y generally is a single bond, O, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene or one of said groups containing 1 to 3, usually 1, heteroatoms selected from O, S or NR¹¹. Examples include -O(CH₂)₁₋₅-, -(CH₂)₁₋₄-O-(CH₂)₁₋₄-, -S-(CH₂)₁₋₅-, -(CH₂)₁₋₄-S-(CH₂)₁₋₄-, -NR¹¹-(CH₂)₁₋₅-, -(CH₂)₁₋₄-NR¹¹-(CH₂)₁₋₄ or C₃₋₁₀ cycloalkylidene. Typically, Y is -OCH₂-, -CH₂O-, C₁₋₂ alkylene, C₂₋₃ alkenylene, C₂₋₃ alkynylene, O or a bond, but usually a bond.

In general, YR^1 is not any one of H, an unsubstituted C_{3-10} cycloalkyl or C_1 - C_6 alkyl. Typically YR^1 is halo or halomethyl-substituted (typically trihalomethyl) phenyl (and usually 1 to 2 substituents in ortho or meta).

X usually is alkylene, alkynylene or alkenylene, typically alkylene, or said
5 hydrocarbons having an intrachain heteroatom, typically O or S. Examples include $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as $-CH=CH-CH_2-$) and C_{2-6} alkynylene. Usually, X is methylene.

R^3 generally is aryl or a heterocycle, typically an aromatic heterocycle. The
10 heterocycle generally will contain 1, 2 or 3 N, S or O atoms in the ring, usually is linked to X through a ring carbon atom and typically contains 4 to 6, usually 5, total ring atoms. The R^3 aryl or heterocycle ordinarily is substituted with 1, 2 or 3, usually 1, R^{17} . R^3 optionally is not indolyl.

When R^3 is substituted with R^{17} then R^{17} typically is aryl or a heterocycle
15 further substituted with 1 or more, usually 1, 2 or 3, R^{19} .

R^{17} is M-Q in some embodiments of the invention. M is a ring. This means
any cyclic organic structure, whether carbocyclic or heterocycle, and whether saturated, unsaturated or aromatic or single or fused ring systems. M is chosen from rings that are structurally stable in biological systems. In general, M is a aryl
20 or aromatic heterocycle where heterocycle is defined above.

Q is a spacer group or bond, and is not critical. Typically it is not cyclic and contains from 0 to 6 atoms, generally H, C, NR^{11} , O or S, usually C, H and O. A typical embodiment is alkyl having 1 to 6 carbons, normal or secondary, optionally with O or NR^{11} replacing 1 methylene group. Generally Q is 1 to 6
25 atoms, usually 1 to 3. Q typically is not substituted with R^{19} , but if it is then typically it is substituted with one R^{19} . R^{19} as substituted on Q usually is alkoxy, halogen, nitro or cyano.

R^{17} typically is selected from the group consisting of C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide,

arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy (optionally an benzyloxy);
 arylalkylthio (optionally a benzylthio); a heterocycle; C₁₋₁₈ hydroxyalkyl, but
 typically is an aryl or a heterocycle, and where each of said aryl, aryloxy, arylthio,
 arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio,
 5 or heterocycle is optionally substituted with 1 or more R¹⁹. R¹⁷ generally is
 positioned distally to X. Optionally, R¹⁷ is not C(O) R¹⁸.

R⁹ and R¹⁸ typically are H, OH or alkyl. R¹⁸ optionally is not NR¹⁵R¹⁶.

R⁵ typically is not present.

R⁶ generally is halogen. Optionally, R⁶ is not C(O) R¹⁸.

10 R⁷, R⁸, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R²⁰, R²¹, R²³ and R²⁴ typically are
 independently H or C₁₋₁₈ alkyl.

R¹² and R²² typically are independently OH or alkyl.

R¹⁹ usually is H; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; C₁₋₁₈ alkoxy; alkenyloxy;
 alkynyloxy; C₁₋₁₈ alkylthio; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; C₄₋₁₀ cycloalkynyl;
 15 halogen; OH; CN; cyanoalkyl; NO₂; NR²⁰R²¹; haloalkyl; haloalkyloxy; C(=O)R¹⁸;
 C(=O)OR¹⁸; OalkenylC(=O)OR¹⁸; -OalkylC(=O)NR²⁰R²¹; aryl; heterocycle;
 -OalkylOC(=O)R¹⁸; C(=O)N(C₁₋₆ alkyl), N(H)S(O)(O)(C₁₋₆ alkyl); arylalkyloxy;
 aryloxy; arylalkyloxy; and arylalkyl; each of which is unsubstituted or
 substituted with 1 or more =O; NR²⁰R²¹; CN; alkoxy; heterocycle; haloalkyl- or
 20 alkyl-substituted heterocycle; heterocycle linked to R¹⁷ by alkyl; alkoxyalkoxy or
 halogen. R¹⁸ as a substituent in R¹⁹ is generally not H. R¹⁹ typically is
 independently halogen, N(R²⁰ R²¹), unsubstituted or heterocycle (O-containing) –
 substituted C₁-C₁₈ alkyl or alkynyl where methylene is substituted with 1-3
 oxygen atoms, or is halo-substituted alkyl or alkoxy.

25 R²⁵ and R²⁶ usually are not present but, if they are, then typically they are
 cyclopentyl or cyclohexyl. If the compound is substituted at R²⁵ or R²⁶, either R² or
 R⁴ is selected from =O, =S, and =NR²⁷, usually =O.

M typically is an aromatic ring, usually single or two fused rings, and containing 4 to 10 atoms. Usually, M is hydrocarbon, but also optionally comprises 1 to 3 N, O and/or S heteroatoms.

Substituents optionally are designated with or without bonds. Regardless
 5 of bond indications, if a substituent is polyvalent (based on its position in the structure referred to), then any and all possible orientations of the substituent are intended.

Haloalkyl or haloalkyloxy typically are $-\text{CF}_3$ or $-\text{OCF}_3$.

In certain embodiments of the compound of formula (A) (a) YR^1 is not H;
 10 (b) R^2 is not OH, SH, =O or =S; (c) R^4 is not =O or =S; (d) YR^1 contains at least one aryl; (e) X is CH_2 ; (f) R^3 contains at least one aryl; (g) if Y is a bond and R^1 is an aryl, this aryl is not phenyl substituted with OH and optionally substituted with methyl, methoxy, nitro, dimethylamino, Cl, Br, or F; (h) if Y is a bond and R^1 is aryl which is para substituted with OH and optionally further substituted with
 15 methyl, methoxy, nitro, diethylamino, Cl, Br or F and X is an alkylene, then R^3 is not a heterocycle containing N; (i) if Y is a bond or $(\text{CH}_2)_{1-6}$, R^1 is H, X is CH_2 and R^3 is phenyl with 1R^{17} , wherein R^{17} is $\text{C}(=\text{O})\text{R}^{18}$, then R^{18} is selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $\text{NR}^{15}\text{R}^{16}$; aryl, or an amino acid residue linked through an amino group thereof; (j) R^{18} is not a C_{3-10} cycloalkyl or C_{4-10} cycloalkenyl;
 20 (k) if Y is a bond or $(\text{CH}_2)_{1-6}$, then R^1 is an aryl unsubstituted or substituted with one or more R^6 , heterocycle unsubstituted or substituted with one or more R^6 , C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6 ; (l) $-\text{YR}^1$ is not H or C_{1-6} alkyl; (m) if Y is a bond or $(\text{CH}_2)_{1-6}$, R^1 is H, and R^3 is a 5 membered heterocycle
 25 with one R^{17} , wherein R^{17} is $\text{C}(=\text{O})\text{R}^{18}$ and R^{18} is $\text{NR}^{15}\text{R}^{16}$, then R^{15} and R^{16} are not a C_{1-18} alkyl or a cycloalkyl; (n) if Y is a bond or $(\text{CH}_2)_{1-6}$, and R^1 is H, and R^3 is a 5 membered heterocycle with one R^{17} , wherein R^{17} is $\text{C}(=\text{O})\text{R}^{18}$ then R^{18} is selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; aryl or an amino acid residue linked through an amino group thereof; (o) R^{18} is

not $\text{NR}^{15}\text{R}^{16}$; (p) if Y is a bond or $(\text{CH}_2)_{1-6}$, R^1 is H, X is $-\text{CH}_2-$ and R^3 is phenyl substituted with one R^{17} , then R^{17} is independently selected from the group hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $\text{C}(=\text{S})\text{R}^{18}$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} ; (q) R^{17} is not $\text{C}(=\text{O})\text{R}^{18}$; (r) if Y is a bond or $(\text{CH}_2)_{1-6}$, and R^1 is H, and R^3 is a 5 membered heterocycle with one R^{17} , wherein R^{17} is $\text{C}(=\text{O})\text{R}^{18}$, then R^{18} is selected from H; OH; C_{1-18} alkyl; aryl, $\text{NR}^{15}\text{R}^{16}$; (s) R^{18} is not C_{1-18} alkoxy; (t) if Y is a bond or $(\text{CH}_2)_{1-6}$, and R^1 is H, and R^3 is a 5 membered heterocycle with one R^{17} , wherein R^{17} is $\text{C}(=\text{O})\text{R}^{18}$, then R^{18} is selected from OH; C_{1-18} alkyl; C_{1-18} alkoxy; aryl, or $\text{NR}^{15}\text{R}^{16}$; (t) R^{18} is not H; (u) if Y is a bond, R^1 is hydrogen, X is an alkyl and R^3 is an aryl thio substituted with 3 R^{17} , and 1 R^{17} is OH in para, then the remaining R^{17} are independently selected from the group consisting of hydrogen; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $\text{C}(=\text{O})\text{R}^9$; $\text{C}(=\text{S})\text{R}^9$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} ; (v) R^{17} is not a C_{1-18} alkyl; (w1) if Y is a bond, R^1 is a hydrogen, X is $-(\text{CH}_2-\text{CH}_2)-$, then R^3 is selected from aryl; aryloxy; aryl- $\text{NR}^{10}-$; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; and each of said aryl, aryloxy, aryl- $\text{NR}^{10}-$, 5 or 6

membered heterocycle, oxyheterocycle or thioheterocycle is optionally substituted with one or more R^{17} ; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms; (w2) R^3 is not an arylthio; (x) if X is $-(CH_2CH_2)_n-S$, R^3 is not an aryl; (y) if Y is a bond, R^1 is H, X is an alkylene and R^3 is phenoxy, R^{17} is independently selected from the group hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; arylthio; arylalkyl (except benzyl); arylalkyloxy (except oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle or C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} ; (z) if R^3 is phenoxy, R^{17} is not benzyl, phenoxy or oxybenzyl; (aa) if XR^3 is fluorobenzyl, R^2 , R^3 , R^4 are $R^1=H$ and Y is NR^{11} , R^{11} is selected from H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; 5-6 membered heterocycle or an amino acid residue linked through a carboxyl group thereof; (bb) R^{11} is not methyl or $C(=O)R^{12}$; (cc) if X is CH_2 and R^3 is a phenyl substituted in para with Cl, and Y is CH_2 , then R^1 is not piperazinyl; (dd) if X is CH_2 and R^3 is a phenyl substituted in para with Cl, and Y is CH_2 , then R^1 heterocycle is aromatic; (ee) if R^5 is an aryl, aryloxy or benzyl group, R^1 is not H or C_{3-10} alkyl; (ff) if R^1 is H or C_{3-10} alkyl, then R^5 is absent or is selected from hydrogen, C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; arylthio; arylalkyl (except benzyl); C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; (gg) R^5 is not aryl, aryloxy or benzyl; (hh) YR^1 is not hydrogen,

unsubstituted C₃₋₁₀ cycloalkyl, or C₁₋₆ alkyl; (ii) YR¹ is not phenyl para substituted with OH; (jj) if R¹ is not H, Y is not NR¹¹ with R¹¹ is C₁₋₆ alkyl or methyl; (kk) YR¹ is not monomethylamino; (ll) if R¹ is a phenyl substituted with one R⁶, then R⁶ is C(=O)R¹⁸ and R¹⁸ is t-butoxy; (mm) R¹ is not piperidinyl and is not piperazinyl
5 substituted with methyl; (nn) YR¹ is not one of the substituents designated R¹³ in column 5, lines 22-38 of U.S. Patent No. 5,486,525 or its family members; (oo) R² and/or R⁵ are none of the substituents collectively designated R¹⁴ and R¹⁵ in column 5, lines 38-53 of U.S. Patent No. 5,486,525 or its family members; (pp) XR³ is not the substructure -(CH₂)_n-Het-C(O)-N(R¹)(R²) using the group designations
10 set forth on column 1, line 41 to column 2 line 24 of U.S. Patent No. 4,990,518 and the comparable disclosure in any member of the patent family of U.S. Patent No. 4,990,518; (qq) XR³ is not the substructure -(CH₂)_n-Y-C(O)-N(R¹)(R²) using the group designations set forth on column 1, line 49 to column 2 line 38 of U.S. Patent No. 5,302,601 and the comparable disclosure in any member of the patent
15 family of U.S. Patent No. 5,302,601; (rr) R² and R⁴ are not both =O or =S; and/or (alone or in any combination) (ss) R⁵ contains none of the substituents designated as « Ar » in WO 00/39127 (incorporated expressly herein by reference), in particular aryl, aryl phenoxy, or benzyl; (tt) YR¹ optionally is not a non-aromatic heterocyclic ring containing 5 or 6 total ring atoms and 1 or 2 N atoms; (uu) YR¹
20 optionally is not a non-aromatic heterocyclic ring containing 1 or 2 N atoms wherein one of the N atoms is linked to the imidazole ring; (vv) YR¹ optionally is not a 5-membered non-aromatic heterocyclic ring which contains 1 N atom and is substituted with amino; (ww) R²⁶ optionally is not normal or secondary alkyl, or benzyl.

25 The exclusions or embodiments herein are not to be interpreted as teaching or suggesting any preferability or lack thereof for any use of the compounds herein, but instead are merely subgeneric designations.

Optionally, the compounds of this invention also exclude all methylene homologues of heretofore known compounds.

According to a particular aspect, the present invention relates to compounds of the formula (A) wherein R^1 is a phenyl optionally substituted with a benzyloxy, and wherein R^{19} at meta is phenyl optionally substituted with a halogen, (particularly chloro) in para, and R^{19} at ortho is H, nitro, amino, mono- or
5 di(C_{1-6} alkyl)-substituted amino, $NHC(O)(C_{1-6}$ alkyl); methoxysulfonamide or $C(O)R^{22}$, wherein R^{22} is $NR^{23}R^{24}$ as defined below. Optionally R^{23} and R^{24} are C_{1-6} alkyl taken together to form a hydroxy-substituted 6-membered saturated N-heterocycle.

An embodiment of the present invention relates to compounds of formula
10 (A) of this invention, pharmaceutically acceptable compositions, salts, tautomers, and isomers thereof and their antiviral uses, wherein:

U is N;

R^1 is selected from phenyl substituted with 0-3 R^6 ; 5 or 6 membered heterocycle containing 1-3 heteroatoms selected from the group O, N, and S,
15 substituted with 0-2 R^6 ; 1-naphthyl substituted with 0-3 R^6 ; 2-naphthyl substituted with 0-3 R^6 ; C_{3-7} cycloalkyl; C_{4-10} cycloalkenyl;

R^2 , R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; CF_3 ; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl, or in the
20 case of R^5 optionally is unsubstituted;

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$;

R^3 is selected from phenyl substituted with 0-3 R^{17} ; (benzoannellated) 5 or 6 membered aromatic heterocycle containing 1-3 heteroatoms selected from the
25 group O, N, and S, substituted with 0-2 R^{17} ; 1-naphthyl substituted with 0-3 R^{17} ; 2-naphthyl substituted with 0-3 R^{17} ; C_{3-7} cycloalkyl; C_{4-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen;

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2 ; $NR^{13}R^{14}$; OCF_3 ; CF_3 ; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl;

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$; alternatively, R^7 and R^8 , together with the nitrogen to which they are attached, combine to form a 5-6 membered ring;

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl;

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl;

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl; and

Y is a bond.

One embodiment of a second aspect of the present invention relates to compounds according to the general formula (A), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof, and their antiviral uses, wherein:

U is N;

R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6 , heterocycle unsubstituted or substituted with one or more R^6 , C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6 ;

Y is selected from the group consisting of a single bond, O; $S(O)_m$ (where m is an integer from 0 to 2); NR^{11} ; and a divalent, saturated or unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain, said heteroatoms being selected from the groups consisting of O, S, and N; such as C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}-$ and C_{3-10} cycloalkylidene;

Each R^2 and R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_{1-10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as $-CH=CH-CH_2-$), C_{2-6} alkynylene;

R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl- $NR^{10}-$; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;; and each of said aryl, aryloxy, arylthio, aryl- $NR^{10}-$, 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle is optionally substituted with one or more R^{17} ; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

R^5 is independently absent or selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

Each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ;

OCF₃; haloalkyl; C(=O)R⁹; C(=S)R⁹; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C₁₋₁₈ hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C₁₋₁₈ hydroxyalkyl is optionally substituted with 1 or more R¹⁹.

Each R⁷ and R⁸ is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₁₋₁₈ alkenyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; 5-6 membered heterocycle; C(=O)R¹²; C(=S) R¹²; an amino acid residue linked through a carboxyl group thereof; alternatively, R⁷ and R⁸, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocycle;

Each R⁹ and R¹⁸ is independently selected from the group consisting of H; OH; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; C₁₋₁₈ alkoxy; NR¹⁵R¹⁶; aryl an amino acid residue linked through an amino group thereof;

Each R¹⁰ and R¹¹ is independently selected from the group the group consisting of H; C₁₋₁₈ alkyl; C₁₋₁₈ alkenyl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; aryl; C(=O)R¹²; 5-6 membered heterocycle; an amino acid residue linked through a carboxyl group thereof;

R¹² is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; an amino acid residue linked through an amino group thereof;

Each R¹⁵ and R¹⁶ is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;

R¹⁹ is independently selected from the group consisting of H; C₁₋₁₈ alkyl, preferably C₁₋₆ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; C₁₋₁₈ alkoxy, preferably C₁₋₆ alkoxy; C₁₋₁₈ alkylthio; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; C₄₋₁₀ cycloalkynyl; halogen; OH; CN; NO₂; NR²⁰R²¹; OCF₃; haloalkyl; C(=O)R²²; C(=S)R²²; SH; C(=O)N(C₁₋₆ alkyl),

N(H)S(O)(O)(C₁₋₆ alkyl); aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle each unsubstituted or substituted with 1 or
 5 more halogens;

Each R²⁰ and R²¹ is independently selected from the group consisting of H; C₁₋₁₈ alkyl, preferably C₁₋₆ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; C(=O)R¹², C(=S)R¹²;

R²² is independently selected from H; OH; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₁₋₁₈ alkoxy; NR²³R²⁴; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl;
 10

Each R²³ and R²⁴ is independently selected from the group the group consisting of H; C₁₋₁₈ alkyl, preferably C₂₋₃ alkyl, wherein C₂₋₃ alkyl taken together with N of R²² can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue.

15 An embodiment relating to a third aspect of the present invention relates to compounds according to the general formula (A), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof, and their antiviral uses, wherein:

20 U is N;

R¹ is selected from hydrogen; phenyl unsubstituted or substituted with 1-3 R⁶; 5 or 6 membered heterocycle, optionally benzo-added, containing 1-3 heteroatoms selected from the group O, N, and S, unsubstituted or substituted with 1-2 R⁶; 1-naphthyl unsubstituted or substituted with 1-3 R⁶; 2-naphthyl
 25 unsubstituted or substituted with 1-3 R⁶; C₃₋₁₀ cycloalkyl, particularly C₃₋₇ cycloalkyl; C₅₋₇ cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen;

Y is selected from the group -(CH₂)₀₋₆-; O; S; NR¹¹; -CH(CH₃)-; -OCH₂-; -CH₂O-; -OCH₂-CH₂-; -CH₂-CH₂O-; -CH₂-O-CH₂-; -(CH₂)₀₋₅-S-; -S-(CH₂)₀₋₅-; -(CH₂)₀₋₂-S-(CH₂)₀₋₂-; -NR¹¹-(CH₂)₀₋₅-; -(CH₂)₀₋₅-NR¹¹-; -CH₂-NR¹¹-CH₂-; -C(CH₃)₂-; (cis or trans)
 30

-CH₂-CH=CH-; (cis or trans) -CH=CH-CH₂-;

Each R², R⁴ and R⁵ is independently selected from hydrogen; straight or branched C₁₋₁₈ alkoxy, particularly C₁₋₆ alkoxy; straight or branched C₁₋₁₈ alkyl particularly C₁₋₆ alkyl; F; Cl; Br; I; OH; CN; NO₂; NR⁷R⁸; OCF₃; CF₃; C(=O)R⁹; phenyl; phenoxy; benzyl; hydroxymethyl or, in the case of R⁵, optionally is absent;

X is selected from the group -CH₂-; -CH(CH₃)-; -CH₂-CH₂-; -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-; -OCH₂-CH₂-; -SCH₂-CH₂-; -NR¹⁰-CH₂-CH₂-; C₃₋₇ cycloalkylidene; -C(CH₃)₂-; -CH₂-CH(CH₃)-CH₂-; -CH(CH₃)-CH₂-CH₂-; -CH₂-CH₂-CH(CH₃)-; -CH=CH-CH₂-;

R³ is selected from unsubstituted or phenyl substituted with 1-3 R¹⁷; 5 or 6 membered heterocycle, containing 1-3 heteroatoms selected from the group O, N, and S, unsubstituted or substituted with 1-2 R¹⁷; 1-naphthyl unsubstituted or substituted with 1-3 R¹⁷; 2-naphthyl unsubstituted or substituted with 1-3 R¹⁷; C₃₋₁₀ cycloalkyl, particularly C₃₋₇ cycloalkyl; C₅₋₇ cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen;

Each R⁶ and R¹⁷ is independently selected from the group H; straight or branched C₁₋₆ alkoxy; straight or branched C₁₋₆ alkyl; F; Cl; Br; I; OH; CN; NO₂; NR¹³R¹⁴; OCF₃; CF₃; C(=O)R¹⁸; unsubstituted phenyl or phenyl substituted with 1-3 R¹⁹; 5 or 6 membered heterocycles, optionally benzo-added, containing 1-3 heteroatoms selected from O, N and S, unsubstituted or substituted with 1 or 2 R¹⁹; 2-naphthyl unsubstituted or substituted with 1-3 R¹⁹; C₃₋₇ cycloalkyl; C₅₋₇ cycloalkenyl, phenoxy; benzyl; hydroxymethyl;

Each R⁷ and R⁸ is independently selected from H; straight or branched C₁₋₁₈ alkyl, preferably C₁₋₆ alkyl; phenyl; C(=O)R¹²; alternatively, R⁷ and R⁸, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring;

Each R^9 and R^{18} is independently selected from H; OH; straight or branched C_{1-18} alkyl, preferably C_{1-6} alkyl; straight or branched C_{1-18} alkoxy, preferably C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl;

Each R^{10} and R^{11} is independently selected from the group H; C_{1-18} alkyl, preferably C_{1-6} straight or branched alkyl; phenyl;

Each R^{12} is selected from the group H; C_{1-18} alkyl, preferably C_{1-6} straight or branched alkyl; phenyl;

Each R^{13} and R^{14} is independently selected from H; straight or branched C_{1-18} alkyl, preferably C_{1-6} alkyl; phenyl; $C(=O)R^{12}$;

Each R^{15} and R^{16} is independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl;

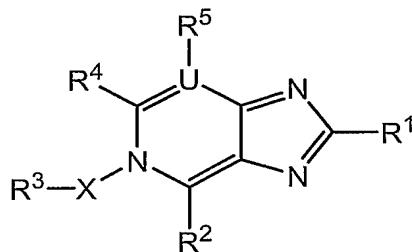
R^{19} is selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl, Br; OH; NO_2 ; $NR^{20}R^{21}$; OCF_3 ; $C(=O)R^{22}$; phenyl; phenoxy; benzyl; hydroxymethyl;

Each R^{20} and R^{21} is independently selected from H; straight or branched C_{1-18} alkyl, preferably C_{1-6} alkyl; phenyl; $C(=O)R^{12}$;

R^{22} is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-18} alkoxy, preferably C_{1-6} alkoxy; $NR^{23}R^{24}$; phenyl;

Each R^{23} and R^{24} is independently selected from the group H; C_{1-18} alkyl, preferably C_{1-6} straight or branched alkyl; phenyl.

An embodiment of a fourth aspect of the present invention relates to compounds of formula (A1) wherein R^1 is directly linked to the imidazo[4,5-d]pyrimidine ring structure, pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof and their use in a treatment of viral infection or to manufacture a medicament to treat viral infections, wherein:



(A1)

U is N;

R¹ is selected from phenyl substituted with 0-3 R⁶; 5 or 6 membered heterocycle containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R⁶; 1-naphthyl substituted with 0-3 R⁶; 2-naphthyl substituted with 0-3 R⁶; C₃₋₇ cycloalkyl; C₄₋₁₀ cycloalkenyl;

R², R⁴ and R⁵ are independently selected from hydrogen; straight or branched C₁₋₆ alkoxy; straight or branched C₁₋₆ alkyl; F; Cl; Br; I; OH; CN; NO₂; NR⁷R⁸; OCF₃; CF₃; C(=O)R⁹; phenyl; phenoxy; benzyl; hydroxymethyl or, in the case of R⁵, optionally is absent;

X is selected from the group -CH₂-; -CH(CH₃)-; -CH₂-CH₂-; -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-; -OCH₂-CH₂-; -SCH₂-CH₂-; -NR¹⁰-CH₂-CH₂-; C₃₋₇ cycloalkylidene; -C(CH₃)₂-; -CH₂-CH(CH₃)-CH₂-; -CH(CH₃)-CH₂-CH₂-; -CH₂-CH₂-CH(CH₃)-; -CH=CH-CH₂-;

R³ is selected from phenyl substituted with 0-3 R¹⁷; (benzoannellated) 5 or 6 membered aromatic heterocycle containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R¹⁷; 1-naphthyl substituted with 0-3 R¹⁷; 2-naphthyl substituted with 0-3 R¹⁷; C₃₋₇ cycloalkyl; C₄₋₁₀ cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen;

R⁶ and R¹⁷ are independently selected from the group H; straight or branched C₁₋₆ alkoxy; straight or branched C₁₋₆ alkyl; F; Cl; Br; I; OH; CN; NO₂; NR¹³R¹⁴; OCF₃; CF₃; C(=O)R¹⁸; phenyl; phenoxy; benzyl; hydroxymethyl;

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$ or R^7 and R^8 , together with the nitrogen to which they are attached, combine to form a 5-6 membered ring;

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl;

R^{10} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl;

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl;

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$;

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

An embodiment of a fifth aspect of the present invention relates to compounds of formula (A1), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers and their use in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein:

U is N;

R^1 is selected from phenyl unsubstituted or substituted with 1-3 R^6 ; 5 or 6 membered heterocycle containing 1-3 heteroatoms selected from the group O, N, and S, unsubstituted or substituted with 1-2 R^6 ; 1-naphthyl unsubstituted or substituted with 1-3 R^6 ; 2-naphthyl unsubstituted or substituted with 1-3 R^6 ; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl;

R^2 and R^4 are hydrogen;

R^5 is absent;

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$;

R^3 is selected from phenyl unsubstituted or substituted with 1-3 R^{17} ; (benzoannellated) 5 or 6 membered aromatic heterocycle containing 1-3 heteroatoms selected from the group O, N, and S, unsubstituted or substituted

with 1-2 R¹⁷; 1-naphthyl unsubstituted or substituted with 1-3 R¹⁷; 2-naphthyl substituted with 0-3 R¹⁷; C₃₋₇ cycloalkyl; C₅₋₇ cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen;

Each R⁶ and R¹⁷ is independently selected from the group H; straight or
5 branched C₁₋₆ alkoxy; straight or branched C₁₋₆ alkyl; F; Cl; Br; I; OH; CN; NO₂;
NR¹³R¹⁴; OCF₃; CF₃; C(=O)R⁹; phenyl; phenoxy; benzyl; hydroxymethyl;

R⁹ is selected from H; OH; straight or branched C₁₋₆ alkyl; straight or
branched C₁₋₆ alkoxy; NR¹⁵R¹⁶; phenyl;

R¹² is selected from the group H; C₁₋₆ straight or branched alkyl; phenyl;

10 Each R¹³ and R¹⁴ is independently selected from H; straight or branched C₁₋₆
alkyl; phenyl; C(=O)R¹²; and

Each R¹⁵ and R¹⁶ is independently selected from the group H; C₁₋₆ straight
or branched alkyl; phenyl;

15 An embodiment of present invention in its sixth aspect comprises the
compounds of formula (A1), pharmaceutically acceptable compositions salts,
tautomers, and isomers thereof and their use in a treatment of viral infection or to
manufacture a medicament to treat viral infection, wherein:

U is N;

20 R¹ is selected from phenyl unsubstituted or substituted with 1-3 R⁶; 5 or 6
membered heterocycle containing 1-3 heteroatoms selected from the group O, N,
and S, unsubstituted or substituted with 1-2 R⁶; 1-naphthyl unsubstituted or
substituted with 1-3 R⁶; 2-naphthyl unsubstituted or substituted with 1-3 R⁶;

R² and R⁴ are hydrogen;

25 R⁵ is absent;

X is selected from -CH₂-; -CH(CH₃)-; -CH₂-CH₂-CH₂-; -OCH₂-CH₂-;
-CH=CH-CH₂;

R³ is selected from phenyl unsubstituted or substituted with 1-3 R¹⁷; 5 or 6
membered aromatic heterocycle containing 1-3 heteroatoms selected from the

group O, N, and S, unsubstituted or substituted with 1-3 R¹⁷; 1-naphthyl unsubstituted or substituted with 1-3 R¹⁷; 2-naphthyl unsubstituted or substituted with 1-3 R¹⁷;

Each R⁶ and R¹⁷ is independently selected from the group H; straight or
 5 branched C₁₋₆ alkoxy; straight or branched C₁₋₆ alkyl; F; Cl; Br; I; OH; CN; NO₂; NR¹³R¹⁴; OCF₃; CF₃; C(=O)R⁹; phenyl; phenoxy; benzyl; hydroxymethyl;

R⁹ is selected from H; OH; straight or branched C₁₋₆ alkyl; straight or branched C₁₋₆ alkoxy; NR¹⁵R¹⁶; phenyl;

R¹² is selected from the group H; C₁₋₆ straight or branched alkyl; phenyl;

10 Each R¹³ and R¹⁴ is independently selected from H; straight or branched C₁₋₆ alkyl; phenyl; C(=O)R¹²; and

Each R¹⁵ and R¹⁶ is independently selected from the group H; C₁₋₆ straight or branched alkyl; and phenyl.

15 An embodiment of present invention in its seventh aspect comprises compounds of formula (A1), pharmaceutically acceptable compositions, salts, tautomers, and isomers thereof and their use in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein:

U is N;

20 R¹ is selected from phenyl unsubstituted or substituted with 1-3 R⁶; 5 or 6 membered heterocycle containing 1-3 heteroatoms selected from the group O, N, and S, unsubstituted or substituted with 1-2 R⁶; 1-naphthyl unsubstituted or substituted with 1-3 R⁶; 2-naphthyl unsubstituted or substituted with 1-3 R⁶;

R² and R⁴ are hydrogen;

25 R⁵ is absent;

X is selected from -CH₂-; -CH(CH₃)-; -CH₂-CH₂-CH₂-; -OCH₂-CH₂-; -CH=CH-CH₂-;

R³ is selected from phenyl unsubstituted or substituted with 1-3 R¹⁷; 5 or 6 membered aromatic heterocycle containing 1-3 heteroatoms selected from the

group O, N, and S, unsubstituted or substituted with 1-2 R^{17} ; 1-naphthyl substituted with 0-3 R^{17} ; 2-naphthyl unsubstituted or substituted with 1-3 R^{17} ;

Each R^6 and R^{17} is independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2 ; $NR^{13}R^{14}$; OCF_3 ; CF_3 ; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl;

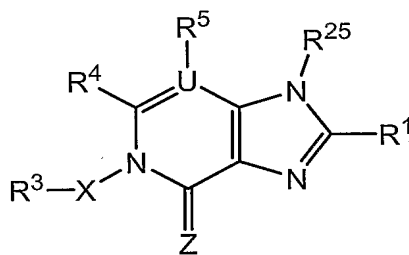
R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl;

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl;

Each R^{13} and R^{14} is independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$; and

Each R^{15} and R^{16} is independently selected from the group H; C_{1-6} straight or branched alkyl; and phenyl.

An embodiment of the present invention in its eighth aspect relates to compounds of the formula (A2), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof and their use in a treatment of viral infection or to manufacture a medicament to treat viral infection



(A2)

wherein

U is N;

R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6 , heterocycle unsubstituted or substituted with one or more R^6 , C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6 ;

X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C_{1-10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected
 5 from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene (such as $-CH=CH-CH_2-$), C_{2-6} alkynylene;

R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl- $NR^{10}-$;
 10 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;; and each of said aryl, aryloxy, arylthio, aryl- $NR^{10}-$, 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle is optionally substituted with one or more R^{17} ; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene,
 15 an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10}
 20 cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; optionally R^4 is not -OH, -SH, =O or =S;

R^5 is independently absent or selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10}
 25 cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

Each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10}
 30 cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ;

OCF₃; haloalkyl; C(=O)R⁹; C(=S)R⁹; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C₁₋₁₈ hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C₁₋₁₈ hydroxyalkyl is optionally substituted with 1 or more R¹⁹;

Each R⁷ and R⁸ is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₁₋₁₈ alkenyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; 5-6 membered heterocycle; C(=O)R¹²; C(=S) R¹²; an amino acid residue linked through a carboxyl group thereof; alternatively, R⁷ and R⁸, together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocycle;

Each R⁹ and R¹⁸ is independently selected from the group consisting of H; OH; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; C₁₋₁₈ alkoxy; NR¹⁵R¹⁶; aryl an amino acid residue linked through an amino group thereof;

Each R¹⁰ and R¹¹ is independently selected from the group the group consisting of H; C₁₋₁₈ alkyl; C₁₋₁₈ alkenyl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; aryl; C(=O)R¹²; 5-6 membered heterocycle; an amino acid residue linked through a carboxyl group thereof;

R¹² is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; an amino acid residue linked through an amino group thereof;

Each R¹³ and R¹⁴ is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; C(=O)R¹²; C(=S)R¹²; an amino acid residue linked through a carboxyl group thereof;

Each R¹⁵ and R¹⁶ is independently selected from the group consisting of H; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; aryl; C₃₋₁₀ cycloalkyl; C₄₋₁₀ cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;

R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2 ; $NR^{20}R^{21}$; OCF_3 ; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6} \text{ alkyl})$,
 5 $N(H)S(O)(O)(C_{1-6} \text{ alkyl})$; aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle each unsubstituted or substituted with 1 or more halogens;

10 Each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;

R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl, ; C_{4-10} cycloalkenyl;

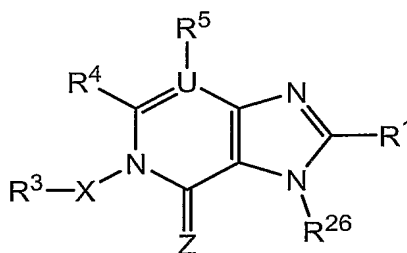
15 Each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;

Z is selected from $(=O)$, $(=S)$, and $(=NR^{27})$;

20 R^{25} is selected from the group consisting of of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; $(C_{3-8} \text{ cycloalkyl})-C_{1-3}$ alkyl; aryl, such as phenyl; 5 or 6 membered heterocycle, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, $(C_{3-8} \text{ cycloalkyl})-C_{1-3}$ alkyl, C_{5-10} bicycloalkyl,
 25 adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , oxybenzyl, and OH; and heterocycle having 3 to 7 carbon atoms, preferably a saturated heterocycle wherein the heteroatoms are S, S(O), or S(O)₂ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocycle carbon atoms; and

R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)- C_{1-6} alkyl; aryl; arylalkyl, such as benzyl.

An embodiment of the present invention in its ninth aspect relates to
 5 compounds of the formula (A3), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof and their use in a treatment of viral infection or to manufacture a medicament to treat viral infection



(A3)

wherein

U is N;

R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or
 15 more R^6 , heterocycle unsubstituted or substituted with one or more R^6 , C_{3-10} cycloalkyl unsubstituted or substituted with one or more R^6 and C_{4-10} cycloalkenyl unsubstituted or substituted with one or more R^6 ;

X is selected from the group consisting of a divalent, saturated or
 20 unsaturated, substituted or unsubstituted C_1-C_{10} hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C_{1-6} alkylene, (for example $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene
 25 (such as $-CH=CH-CH_2-$), C_{2-6} alkynylene;

R^3 is selected from the group consisting of aryl; aryloxy; arylthio; aryl- NR^{10} -; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;; and each of said aryl, aryloxy, arylthio, aryl- NR^{10} -, 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle is optionally substituted with one or more R^{17} ; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

R^4 is independently selected from the group consisting of hydrogen C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN ; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; optionally, R^4 is not OH, SH, thio or oxo;

R^5 is independently absent or selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN ; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

Each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN ; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} ;

Each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocycle; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8 , together with the nitrogen to which they
 5 are attached, combine to form a 5-6 membered heterocycle;

Each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;

Each R^{10} and R^{11} is independently selected from the group the group
 10 consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocycle; an amino acid residue linked through a carboxyl group thereof;

R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked
 15 through an amino group thereof;

Each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;

R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2 ; $NR^{20}R^{21}$; OCF_3 ; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6} \text{ alkyl})$, $N(H)S(O)(O)(C_{1-6} \text{ alkyl})$; aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a
 20 phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle each unsubstituted or substituted with 1 or
 25 more halogens;

Each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;

R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl;

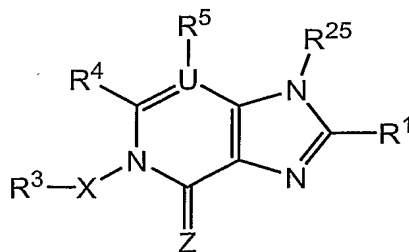
Each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;

Z is selected from $(=O)$, $(=S)$, and $(=NR^{27})$;

R^{26} is selected from the group consisting of of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; $(C_{3-8}$ cycloalkyl)- C_{1-3} alkyl; aryl, such as phenyl; 5 or 6 membered heterocycle, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, $(C_{3-8}$ cycloalkyl)- C_{1-3} alkyl, C_{5-10} bicycloalkyl, adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , oxybenzyl, and OH; and heterocycle having 3 to 7 carbon atoms, preferably a saturated heterocycle wherein the heteroatoms are S, S(O), or S(O)₂ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocycle carbon atoms; and

R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, $(C_{3-10}$ cycloalkyl)- C_{1-6} alkyl; aryl; arylalkyl, such as benzyl.

An embodiment of the present invention in its tenth aspect relates to compounds of the formula (A2), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof and their use in a treatment of viral infection or to manufacture a medicament to treat viral infection



(A2)

5 wherein

U is N;

R¹ is selected from hydrogen; aryl unsubstituted or substituted with one or more R⁶, heterocycle unsubstituted or substituted with one or more R⁶, C₃₋₁₀ cycloalkyl unsubstituted or substituted with one or more R⁶ and C₄₋₁₀ cycloalkenyl
 10 unsubstituted or substituted with one or more R⁶;

X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C₁₋₁₀ hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected
 15 from the group consisting of O, S, and N; such as C₁₋₆ alkylene, (for example -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-), -(CH₂)₂₋₄-O-(CH₂)₂₋₄-, -(CH₂)₂₋₄-S-(CH₂)₂₋₄-, -(CH₂)₂₋₄-NR¹⁰-(CH₂)₂₋₄-, C₃₋₁₀ cycloalkylidene, C₂₋₆ alkenylene (such as -CH=CH-CH₂-), C₂₋₆ alkynylene;

R² is selected from the group consisting of hydrogen C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; C₁₋₁₈ alkoxy; C₁₋₁₈ alkylthio; halogen; OH; CN; NO₂; NR⁷R⁸; OCF₃; haloalkyl; C(=O)R⁹; C(=S)R⁹; SH; aryl; aryloxy; arylthio; arylalkyl; C₁₋₁₈ hydroxyalkyl; C₃₋₁₀ cycloalkyl; C₃₋₁₀ cycloalkyloxy; C₃₋₁₀ cycloalkylthio; C₃₋₁₀ cycloalkenyl; C₃₋₁₀ cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

25 R³ is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR¹⁰-; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; and each of said aryl, aryloxy, arylthio, aryl-NR¹⁰-, 5 or 6 membered heterocycle, oxyheterocycle or

thioheterocycle is optionally substituted with one or more R^{17} ; C_{3-10} cycloalkyl, oxycycloalkyl or thiocycloalkyl; C_{4-10} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

5 R^5 is independently absent or selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; C_{1-18} hydroxyalkyl; C_{3-10} cycloalkyl; C_{3-10} cycloalkyloxy; C_{3-10} cycloalkylthio C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

Each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; 15 arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C_{1-18} hydroxyalkyl is optionally substituted 20 with 1 or more R^{19} ;

Each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocycle; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8 , together with the nitrogen to which they 25 are attached, combine to form a 5-6 membered heterocycle;

Each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;

Each R^{10} and R^{11} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocycle; an amino acid residue linked through a carboxyl group thereof;

5 R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;

Each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an
10 amino acid residue linked through a carboxyl group thereof;

R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2 ; $NR^{20}R^{21}$; OCF_3 ; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6} \text{ alkyl})$,
15 $N(H)S(O)(O)(C_{1-6} \text{ alkyl})$; aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle each unsubstituted or substituted with 1 or more halogens;

20 Each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;

R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl;

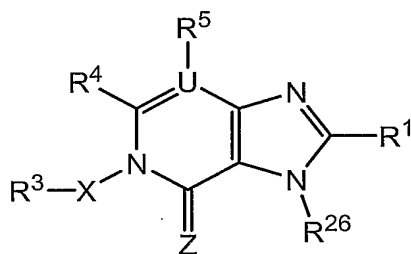
25 Each R^{23} and R^{24} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;

Z is selected from $(=O)$, $(=S)$, and $(=NR^{27})$;

R^{25} is selected from the group consisting of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; (C_{3-8} cycloalkyl)- C_{1-3} alkyl; aryl, such as phenyl; 5 or 6 membered heterocycle, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, (C_{3-8} cycloalkyl)- C_{1-3} alkyl, C_{5-10} bicycloalkyl, adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , oxybenzyl, and OH; and heterocycle having 3 to 7 carbon atoms, preferably a saturated heterocycle wherein the heteroatoms are S, S(O), or S(O)₂ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocycle carbon atoms; and

R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)- C_{1-6} alkyl; aryl; arylalkyl, such as benzyl;

An embodiment of the present invention in its eleventh aspect relates to compounds of the formula (A3), pharmaceutically acceptable compositions, salts, tautomers, polymorphs and isomers thereof and their use in a treatment of viral infection or to manufacture a medicament to treat viral infection



(A3)

wherein:

U is N;

R^1 is selected from hydrogen; aryl unsubstituted or substituted with one or more R^6 , heterocycle unsubstituted or substituted with one or more R^6 , C_{3-10}

cycloalkyl unsubstituted or substituted with one or more R⁶ and C₄₋₁₀ cycloalkenyl unsubstituted or substituted with one or more R⁶;

X is selected from the group consisting of a divalent, saturated or unsaturated, substituted or unsubstituted C₁-C₁₀ hydrocarbon group optionally including one or more heteroatoms in the main chain (provided that the heteroatom is not linked to N of the nucleus), said heteroatoms being selected from the group consisting of O, S, and N; such as C₁₋₆ alkylene, (for example -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-), -(CH₂)₂₋₄-O-(CH₂)₂₋₄-, -(CH₂)₂₋₄-S-(CH₂)₂₋₄-, -(CH₂)₂₋₄-NR¹⁰-(CH₂)₂₋₄-, C₃₋₁₀ cycloalkylidene, C₂₋₆ alkenylene (such as -CH=CH-CH₂-), C₂₋₆ alkynylene;

R² is independently selected from the group consisting of hydrogen C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; C₁₋₁₈ alkoxy; C₁₋₁₈ alkylthio; halogen; OH; CN; NO₂; NR⁷R⁸; OCF₃; haloalkyl; C(=O)R⁹; C(=S)R⁹; SH; aryl; aryloxy; arylthio; arylalkyl; C₁₋₁₈ hydroxyalkyl; C₃₋₁₀ cycloalkyl; C₃₋₁₀ cycloalkyloxy; C₃₋₁₀ cycloalkylthio; C₃₋₁₀ cycloalkenyl; C₃₋₁₀ cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

R³ is selected from the group consisting of aryl; aryloxy; arylthio; aryl-NR¹⁰-; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;; and each of said aryl, aryloxy, arylthio, aryl-NR¹⁰-, 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle is optionally substituted with one or more R¹⁷; C₃₋₁₀ cycloalkyl, oxycycloalkyl or thiocycloalkyl; C₄₋₁₀ cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen; H with the proviso that if X is an alkylene, an alkenylene or an alkynylene, then X comprises at least 5 carbon atoms;

R⁵ is independently absent or selected from the group consisting of hydrogen; C₁₋₁₈ alkyl; C₂₋₁₈ alkenyl; C₂₋₁₈ alkynyl; C₁₋₁₈ alkoxy; C₁₋₁₈ alkylthio; halogen; OH; CN; NO₂; NR⁷R⁸; OCF₃; haloalkyl; C(=O)R⁹; C(=S)R⁹; SH; aryl; aryloxy; arylthio; arylalkyl; C₁₋₁₈ hydroxyalkyl; C₃₋₁₀ cycloalkyl; C₃₋₁₀ cycloalkyloxy; C₃₋₁₀ cycloalkylthio C₃₋₁₀ cycloalkenyl; C₃₋₁₀ cycloalkynyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle;

Each R^6 and R^{17} is independently selected from the group consisting of hydrogen; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl or C_{3-10} cycloalkynyl; halogen; OH; CN; NO_2 ; NR^7R^8 ; OCF_3 ; haloalkyl; $C(=O)R^9$; $C(=S)R^9$; SH; aryl; aryloxy; arylthio; arylalkyl; arylalkyloxy (optionally a oxybenzyl); arylalkylthio (optionally a benzylthio); 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle; C_{1-18} hydroxyalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl, arylalkyloxy (optionally a oxybenzyl), arylalkylthio (optionally a benzylthio), 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle, C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} ;

Each R^7 and R^8 is independently selected from the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; 5-6 membered heterocycle; $C(=O)R^{12}$; $C(=S)R^{12}$; an amino acid residue linked through a carboxyl group thereof; alternatively, R^7 and R^8 , together with the nitrogen to which they are attached, combine to form a 5-6 membered heterocycle;

Each R^9 and R^{18} is independently selected from the group consisting of H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{1-18} alkoxy; $NR^{15}R^{16}$; aryl an amino acid residue linked through an amino group thereof;

Each R^{10} and R^{11} is independently selected from the group the group consisting of H; C_{1-18} alkyl; C_{1-18} alkenyl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; aryl; $C(=O)R^{12}$; 5-6 membered heterocycle; an amino acid residue linked through a carboxyl group thereof;

R^{12} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through an amino group thereof;

Each R^{15} and R^{16} is independently selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; an amino acid residue linked through a carboxyl group thereof;

R^{19} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy, preferably C_{1-6} alkoxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; NO_2 ; $NR^{20}R^{21}$; OCF_3 ; haloalkyl; $C(=O)R^{22}$; $C(=S)R^{22}$; SH; $C(=O)N(C_{1-6} \text{ alkyl})$,
 5 $N(H)S(O)(O)(C_{1-6} \text{ alkyl})$; aryl; aryloxy; arylthio; arylalkyl; and each of said aryl, aryloxy, arylthio, arylalkyl substituted with 1 or more halogens, particularly a phenyl substituted with 1-2 halogens; hydroxyalkyl; 5 or 6 membered heterocycle, oxyheterocycle or thioheterocycle each unsubstituted or substituted with 1 or more halogens;

10 Each R^{20} and R^{21} is independently selected from the group consisting of H; C_{1-18} alkyl, preferably C_{1-6} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; $C(=O)R^{12}$, $C(=S)R^{12}$;

R^{22} is independently selected from H; OH; C_{1-18} alkyl; C_{2-18} alkenyl; C_{1-18} alkoxy; $NR^{23}R^{24}$; aryl; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl;

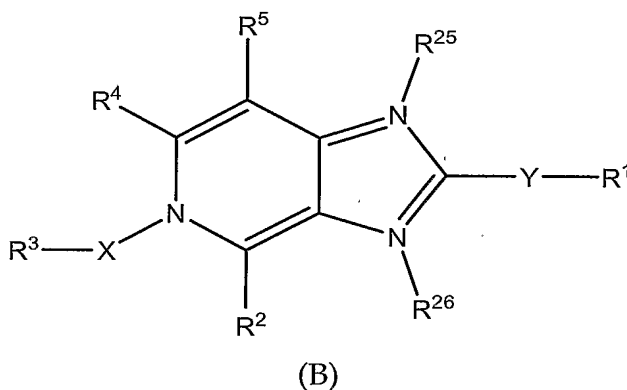
15 Each R^{23} and R^{24} is independently selected from the group the group consisting of H; C_{1-18} alkyl, preferably C_{2-3} alkyl, wherein C_{2-3} alkyl taken together with N of R^{22} can form a saturated heterocycle, which heterocycle is optionally substituted with OH or aryl or an amino acid residue;

Z is selected from $(=O)$, $(=S)$, and $(=NR^{27})$;

20 R^{26} is selected from the group consisting of H, C_{1-18} alkyl, preferably C_{1-4} alkyl; C_{3-10} cycloalkyl, such as C_{5-10} bicycloalkyl; C_{3-10} cycloalkenyl; $(C_{3-8} \text{ cycloalkyl})-C_{1-3}$ alkyl; aryl, such as phenyl; 5 or 6 membered heterocycle, such as pyridyl; alkylaryl, such as benzyl; and each of said C_{1-18} alkyl, preferably C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, $(C_{3-8} \text{ cycloalkyl})-C_{1-3}$ alkyl, C_{5-10} bicycloalkyl,
 25 adamantyl, phenyl, pyridyl and benzyl is optionally substituted with 1-4 of each of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , oxybenzyl, and OH; and heterocycle having 3 to 7 carbon atoms, preferably a saturated heterocycle wherein the heteroatoms are S, S(O), or S(O)₂ separated from the imidazopyridyl ring nitrogen atom by at least 2 heterocycle carbon atoms; and

R^{27} is selected from the group consisting of H, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)- C_{1-6} alkyl; aryl; arylalkyl, such as benzyl.

An embodiment of this invention in its twelfth aspect relates to compounds of the general formula (B), pharmaceutically acceptable compositions, and the
5 antiviral use thereof.



wherein:

R^1 is selected from aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and
10 C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or 2 R^6 ;

Y is a bond;

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸, haloalkyloxy, haloalkyl, -C(=O)R⁹, -C(=S)R⁹, SH, aryl, aryloxy, arylthio,
15 arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from (=O), (=S), and =NR²⁷; provided that R^2 is not OH, SH, thio or oxo;

X is selected from C_{1-3} alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R¹⁰)-, or heterocycle, where each is optionally substituted with at least one R^{17} , provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸,
25

haloalkyloxy, haloalkyl, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=S)R^9$, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl, $-CO_2R^{18}$, NO_2 , $-NR^7R^8$, C_{1-18} haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19} ;

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, $-C(=O)R^{12}$, $-C(=S)R^{12}$, an amino acid residue linked through a carboxyl group thereof, or where R^7 and R^8 together with the nitrogen form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, $-NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, or $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1 - C_{12} alkyl, C_6 - C_{20} aryl, C_6 - C_{20} alkylaryl or C_6 - C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, or an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{17} is independently M-Q- wherein M is a ring optionally substituted with 1 or more R^{19} , and Q is a bond or a linking group connecting M to R^3 having 1 to 10

atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R¹⁹;

R¹⁹ is selected from hydrogen, C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, C₂₋₁₈ alkynyl, C₁₋₁₈ alkoxy, C₂₋₁₈ alkenyloxy, C₂₋₁₈ alkynyloxy, C₁₋₁₈ alkylthio, C₃₋₁₀ cycloalkyl, C₄₋₁₀ cycloalkenyl, C₄₋₁₀ cycloalkynyl, halogen, -OH, -CN, cyanoalkyl, -NO₂, -NR²⁰R²¹, C₁₋₁₈ haloalkyl, C₁₋₁₈ haloalkyloxy, -C(=O)R¹⁸, -C(=O)OR¹⁸, -OalkenylC(=O)OR¹⁸, -OalkylC(=O)NR²⁰R²¹, -OalkylOC(=O)R¹⁸, -C(=S)R¹⁸, SH, -C(=O)N(C₁₋₆ alkyl), -N(H)S(O)(O)(C₁₋₆ alkyl), aryl, heterocycle, C₁₋₁₈ alkylsulfone, arylsulfoxide, arylsulfonamide, aryl(C₁₋₁₈)alkyloxy, aryloxy, aryl(C₁₋₁₈ alkyl)oxy, arylthio, aryl(C₁₋₁₈)alkylthio or aryl(C₁₋₁₈)alkyl, where each may be optionally substituted with 1 or more =O, NR²⁰R²¹, CN, C₁₋₁₈ alkoxy, heterocycle, C₁₋₁₈ haloalkyl, heterocycle alkyl, heterocycle connected to R¹⁷ by alkyl, alkoxyalkoxy or halogen;

R²⁰ and R²¹ are independently selected from hydrogen, C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, C₂₋₁₈ alkynyl, aryl, C₃₋₁₀ cycloalkyl, C₄₋₁₀ cycloalkenyl, -C(=O)R¹², or -C(=S)R¹²;

R²⁵ and R²⁶ are independently not present or are selected from hydrogen, C₁₋₁₈ alkyl, C₃₋₁₀ cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, CH₂OH, benzyloxy, and OH; and

R²⁷ is selected from hydrogen, C₁₋₁₈ alkyl, C₃₋₁₀ cycloalkyl, (C₃₋₁₀ cycloalkyl)-C₁₋₆ alkyl, aryl, and aryl C₁₋₁₈ alkyl, and salts, tautomers, polymorphs, isomers and solvates thereof.

The various embodiments above represent subgeneric groups of compounds. However, it will be understood that the compounds of this invention also comprise other subgeneric classes in which various substituent groups are mixed and matched from any of the foregoing subgeneric groups, i.e., additional classes of compounds falling within the scope of this invention optionally will contain R¹⁹ from the main embodiment (claim 1) but also a

narrower Y group (e.g., Y = bond) from another disclosed embodiment, in any combination or permutation.

Utilities

5 The compounds of this invention, or the metabolites produced from these compounds *in vivo*, have a large number of uses. They are useful in immunology, chromatography, diagnostics and therapeutics, among other fields.

The compounds of the formulas of this invention are conjugated to immunogenic polypeptides as a reagent for eliciting antibodies capable of binding specifically to the polypeptide, to the compounds or to their metabolic products
10 which retain immunologically recognized epitopes (sites of antibody binding). These immunogenic compositions therefore are useful as intermediates in the preparation of antibodies for use in diagnostics, quality control, or the like, or in assays for the compounds of the formulas of this invention or their novel metabolic products. The compounds are useful for raising antibodies against
15 otherwise non-immunogenic polypeptides, in that the compounds serve as haptenic sites stimulating an immune response which cross-reacts with the unmodified conjugated protein.

Conjugates of the compounds of the formulas of this invention with immunogenic polypeptides such as albumin or keyhole limpet hemocyanin
20 generally are useful as immunogens. The polypeptides are conjugated at the same sites denoted for amino acids. The metabolic products described above may retain a substantial degree of immunological cross reactivity with the compounds of the invention. Thus, the antibodies of this invention will be capable of binding to the unprotected compounds of the invention without binding to the protected
25 compounds. Alternatively the metabolic products will be capable of binding to the protected compounds and/or the metabolic products without binding to the protected compounds of the invention, or will be capable of binding specifically to any one or all three. The antibodies desirably will not substantially cross-react with naturally-occurring materials. Substantial cross-reactivity is reactivity under
30 specific assay conditions for specific analytes sufficient to interfere with the assay results.

The immunogens of this invention contain the compound of this invention presenting the desired epitope in association with an immunogenic substance. Within the context of the invention such association means covalent bonding to form an immunogenic conjugate (when applicable) or a mixture of non-covalently bonded materials, or a combination of the above. Immunogenic substances include adjuvants such as Freund's adjuvant, immunogenic proteins such as viral, bacterial, yeast, plant and animal polypeptides, in particular keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin or soybean trypsin inhibitor, and immunogenic polysaccharides. Typically, the compound having the structure of the desired epitope is covalently conjugated to an immunogenic polypeptide or polysaccharide by the use of a polyfunctional (ordinarily bifunctional) cross-linking agent. Methods for the manufacture of hapten immunogens are conventional *per se*, and any of the methods used heretofore for conjugating haptens to immunogenic polypeptides or the like are suitably employed here as well, taking into account the functional groups on the precursors or hydrolytic products which are available for cross-linking and the likelihood of producing antibodies specific to the epitope in question as opposed to the immunogenic substance.

Typically the polypeptide is conjugated to a site on the compound of the invention distant from the epitope to be recognized.

The conjugates are prepared in conventional fashion. For example, the cross-linking agents N-hydroxysuccinimide, succinic anhydride or $\text{alkN}=\text{C}=\text{Nalk}$ are useful in preparing the conjugates of this invention. The conjugates comprise a compound of the invention attached by a bond or a linking group of 1-100, typically, 1-25, more typically 1-10 carbon atoms to the immunogenic substance. The conjugates are separated from starting materials and by products using chromatography or the like, and then are sterile filtered and vialled for storage.

Animals are typically immunized against the immunogenic conjugates or derivatives and antisera or monoclonal antibodies prepared in conventional fashion.

The compounds of this invention are useful as linkers, spacers or affinity (typically hydrophobic) moieties in preparing affinity absorption matrices. The compounds of the invention optionally are bound covalently to an insoluble matrix and used for affinity chromatography separations, depending on the
5 nature of the groups of the compounds, for example compounds with pendant aryl groups are useful in making hydrophobic affinity columns.

They also are useful as linkers and spacers in preparing immobilized enzymes for process control, or in making immunoassay reagents. The compounds herein contain functional groups that are suitable as sites for cross-
10 linking desired substances. For example, it is conventional to link affinity reagents such as hormones, peptides, antibodies, drugs, and the like to insoluble substrates. These insolubilized reagents are employed in known fashion to absorb binding partners for the affinity reagents from manufactured preparations, diagnostic samples and other impure mixtures. Similarly, immobilized enzymes
15 are used to perform catalytic conversions with facile recovery of enzyme. Bifunctional compounds are commonly used to link analytes to detectable groups in preparing diagnostic reagents.

The compounds of this invention are labeled with detectable moieties such as biotin, radioisotopes, enzymes and the like for diagnostic purposes. Suitable
20 techniques for accomplishing the labeling of the compounds of the formulas of this invention are well known and will be apparent to the artisan from consideration of this specification as a whole. For example, one suitable site for labeling is R^{17} or R^{19} .

More typically, however, the compounds of the invention are employed for
25 the treatment or prophylaxis of viral infections such as yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus, but more particularly Flaviviral or Picornaviral infections, in particular, HCV and BVDV.

The therapeutic compound(s) of this invention are administered to a
30 subject mammal (including a human) by any means well known in the art, i.e.

orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization. The therapeutically effective amount of the compound(s) is a Flaviviral or Picornaviral growth inhibiting amount. More preferably, it is a Flaviviral or Picornaviral replication inhibiting amount or a Flaviviral or Picornaviral enzyme inhibiting amount of the compounds of the formulas of this invention. This is believed to correspond to an amount which ensures a plasma level of between about 1 µg/ml and 100 mg/ml, optionally of 10 mg/ml. This optionally is achieved by administration of a dosage of in the range of 0.001 mg to 60 mg, preferably 0.01 mg to 10 mg, preferably 0.1 mg to 1 mg per day per kg bodyweight for humans. These are starting points for determining the optimal dosage of the compound of this invention. The actual amount will depend upon many factors known to the artisan, including bioavailability of the compound, whether it contains a prodrug functionality, its metabolism and distribution in the subject and its potency, among others. It typically is necessary to determine the proper dosing in the clinical setting, and this is well within the skill of the ordinary artisan. The therapeutically effective amount of the compound(s) of this invention optionally are divided into several sub-units per day or are administered at daily or more than one day intervals, depending upon the pathologic condition to be treated, the patient's condition and the nature of the compound of this invention.

As is conventional in the art, the evaluation of a synergistic effect in a drug combination may be made by analyzing the quantification of the interactions between individual drugs, using the median effect principle described by Chou et al. in *Adv. Enzyme Reg.* (1984) 22:27 or tests such as, but not limited to, the isobologram method, as previously described by Elion et al. in *J. Biol. Chem.* (1954) 208:477-488 and by Baba et al. in *Antimicrob. Agents Chemother.* (1984) 25:515-517, using EC₅₀ for calculating the fractional inhibitory concentration.

Suitable anti-viral agents for inclusion in combination antiviral compositions or for coadministration in a course of therapy include, for instance, interferon alpha, ribavirin, a compound falling within the scope of disclosure of EP 1162196, WO 03/010141, WO 03/007945, WO04/005286 and WO 03/010140, a

compound falling within the scope of disclosure of WO 00/204425, and other patents or patent applications within their patent families, in amounts of 1 to 99.9% by weight compound of this invention, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight as can be readily determined by one skilled in the art. Such co-administered agents need not be formulated in the same dosage form as the compound of the invention. They optionally are simply administered to the subject in the course of treatment along with a course of treatment with a compound of formula (A).

The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore, for example in the treatment of BVDV. Veterinary carriers are materials useful for the purpose of administering the composition and are excipients which are otherwise inert or acceptable in the veterinary art and are compatible with the compound of this invention. These veterinary compositions may be administered orally, parenterally or by any other desired route.

The compounds of the invention optionally are bound covalently to an insoluble matrix and used for affinity chromatography (separations, depending on the nature of the groups of the compounds, for example compounds with pendant aryl are useful in hydrophobic affinity separations).

The compounds of the invention are employed for the treatment or prophylaxis of viral infections, more particularly Flaviviral or Picornaviral infections, in particular, HCV and BVDV. When using one or more derivatives of the formula (A) as defined herein:

- the active ingredients of the compound(s) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- the therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans and other mammals, preferably is a Flaviviral or Picornaviral enzyme inhibiting amount. More preferably, it is a Flaviviral or Picornaviral replication inhibiting amount or a

Flaviviral or Picornaviral enzyme inhibiting amount of the derivative(s) of formula (A) as defined herein corresponds to an amount which ensures a plasma level of between 1 µg/ml and 100 mg/ml, optionally of 10 mg/ml. This can be achieved by administration of a dosage of in the range of 0.001 mg to 20 mg, preferably 0.01 mg to 5 mg, preferably 0.1mg to 1 mg per day per kg bodyweight for humans. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

The present invention further relates to a method for preventing or treating a viral infections in a subject or patient by administering to the patient in need thereof a therapeutically effective amount imidazo[4,5-d]pyrimidine derivatives of the present invention. The therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans and other mammals, preferably is a Flaviviral or Picornaviral enzyme inhibiting amount. More preferably, it is a Flaviviral or Picornaviral replication inhibiting amount or a Flaviviral or Picornaviral enzyme inhibiting amount of the derivative(s) of formula (A) as defined herein. Suitable dosage is usually in the range of 0.001 mg to 60 mg, optionally 0.01 mg to 10 mg, optionally 0.1mg to 1 mg per day per kg bodyweight for humans. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

This principle may be applied to a combination of different antiviral drugs of the invention or to a combination of the antiviral drugs of the invention with other drugs that exhibit anti-BVDV or anti-HCV activity.

The invention thus relates to a pharmaceutical composition or combined preparation having synergistic effects against a viral infection and containing:
Either:

A) a combination of two or more of the imidazo[4,5-d]pyrimidine derivatives of the present invention, and

B) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers, for simultaneous, separate or sequential use in the treatment or prevention of a viral infection, or

C) one or more anti-viral agents, and

5 D) at least one of the imidazo[4,5-d]pyrimidine derivatives of the present invention, and

E) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers, for simultaneous, separate or sequential use in the treatment or prevention of a viral infection.

10 Suitable anti-viral agents for inclusion into the synergistic antiviral compositions or combined preparations of this invention include, for instance, interferon- α (either pegylated or not), ribavirin and other selective inhibitors of the replication of BVDV or HCV.

The pharmaceutical composition or combined preparation with synergistic activity against viral infection according to this invention may contain the
15 imidazo[4,5-d]pyrimidine derivatives of the present invention over a broad content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the imidazo[4,5-d]pyrimidine derivatives of the present invention of the combined preparation is within the range of 0.1 to
20 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

According to a particular embodiment of the invention, the compounds of the invention may be employed in combination with other therapeutic agents for the treatment or prophylaxis of Flaviviral or Picornaviral infections, optionally,
25 HCV and BVDV. The invention therefore relates to the use of a composition comprising:

(a) one or more compounds of the formulas of this invention, and

(b) one or more Flaviviral or Picornaviral enzyme inhibitors as biologically active agents in respective proportions such as to provide a
30 synergistic effect against a viral infection, particularly a Flaviviral or Picornaviral infection in a mammal, for instance in the form of a combined preparation for

simultaneous, separate or sequential use in viral infection therapy, such as of HCV, BVDV and Cocksackie virus. Examples of such further therapeutic agents for use in combinations include agents that are effective for the treatment or prophylaxis of these infections, including interferon alpha, ribavirin, a compound
5 falling within the scope of disclosure EP 1162196, WO 03/010141, WO 03/007945, WO04/005286 and WO 03/010140, a compound falling within the scope of disclosure WO 00/204425, and other patents or patent applications within their patent families or all the foregoing filings and/or an inhibitor of Flaviviral protease and/or one or more additional Flavivirus polymerase inhibitors.

10 When using a combined preparation of (a) and (b):

- the active ingredients (a) and (b) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- 15 - the therapeutically effective amount of the combined preparation of (a) and (b), especially for the treatment of viral infections in humans and other mammals, particularly is a Flaviviral or Picornaviral enzyme inhibiting amount. More particularly, it is a Flaviviral or Picornaviral replication inhibiting amount of derivative (a) and a Flaviviral or Picornaviral enzyme
20 inhibiting amount of inhibitor (b). Still more particularly when the said Flaviviral or Picornaviral enzyme inhibitor (b) is a polymerase inhibitor, its effective amount is a polymerase inhibiting amount. When the said Flaviviral or Picornaviral enzyme inhibitor (b) is a protease inhibitor, its effective amount is a protease inhibiting amount.
- 25 - ingredients (a) and (b) may be administered simultaneously but it is also beneficial to administer them separately or sequentially, for instance within a relatively short period of time (e.g. within about 24 hours) in order to achieve their functional fusion in the body to be treated.

The invention also relates to the compounds of the formulas of this
30 invention being used for inhibition of the proliferation of other viruses than BVDV, HCV or Cocksackie virus, particularly for the inhibition of other

flaviviruses or picornaviruses, with in particular yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus, and also for the inhibition of HIV and other retroviruses or lentiviruses.

5 More generally, the invention relates to the compounds of the formulas of this invention being useful as agents having biological activity (particularly antiviral activity) or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells
10 remote from an animal.

Salts and Solvates

 The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms formed by the compounds of the
15 compounds of this invention. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid.

 The compounds of the invention may bear multiple positive or negative
20 charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood
25 that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also
30 forms that are not in association with counter ions (e.g., aqueous or organic solutions).

The compounds of this invention include the solvates formed with the compounds of this invention and their salts, such as for example hydrates, alcoholates and the like. The compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the compounds of this invention with one or more amino acids as described above. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a compound of this invention. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

The compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na⁺, Li⁺, K⁺, Ca⁺² and Mg⁺². Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in

association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li⁺, Na⁺, Ca⁺² and Mg⁺² and K⁺. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, benzoic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, fumaric, tartaric, pyruvic, maleic, malonic, malic, salicylic (i.e. 2-hydroxybenzoic), *p*-aminosalicylic, isethionic, lactobionic, succinic oxalic and citric acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and *p*-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids,. C₁-C₆ alkylsulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic, and the like. Exemplary salts include mesylate and HCl.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX₄⁺ (wherein X is C₁-C₄ alkyl). Physiologically acceptable salts

of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound containing a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X typically is independently selected from H or a $\text{C}_1\text{-C}_4$ alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Isomers

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and stereochemical forms, which the compounds of the formulas of this invention may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of the formulas of this invention may have one or more chiral centers), as well as the stereochemically pure or enriched isomers. More particularly, stereogenic centers may have either the R- or S-configuration, and double or triple bonds optionally are in either the cis- or trans-configuration.

Enriched isomeric forms of a compound of this invention are defined as a single isomer substantially free of the compound's other enantiomers or diastereomers. In particular, the term "stereoisomerically enriched" or "chirally enriched" relates to compounds having a single stereoisomeric proportion of at

least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" contain undetectable levels of any other isomer.

5 Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; 10 Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, 15 and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing an acidic functionality, such as carboxylic 20 acid and sulfonic acid.

 The diastereomeric salts optionally are induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in 25 formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994). Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral 30 derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched

xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric

5 diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases

10 are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCelTM CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the

15 like, modified with an alcohol such as ethanol, isopropanol and the like. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990). "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

20 As used herein and unless otherwise stated, the term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

25 The term "isomers" as used herein means all possible isomeric forms, including tautomeric and stereochemical forms, which the compounds of the formulas of this invention may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative

30 configurations are contemplated as well.. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically

isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of the formulas of this invention may have at least one chiral center) of the basic molecular structure, as well as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either
5 the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term "stereoisomerically pure" or "chirally
10 pure" relates to compounds having a stereoisomeric excess of at least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess,
15 respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents
20 ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with
25 chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl- β -phenylethylamine (amphetamine), and the like with
30 asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional

crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCelTM CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

The terms cis and trans are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents

on a ring moiety. The absolute stereochemical configuration of the compounds of formula (1) may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

5

Metabolites

The present invention also provides the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C14 or H3) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no antiviral activity of their own.

Formulations

The compounds of the invention optionally are formulated with conventional pharmaceutical carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers,

binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and
5 other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be
10 treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates,
15 dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the present invention.
20 They may also include additives such as wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride) and the like, provided the same are consistent with pharmaceutical practice, i.e. carriers and additives which do not create
25 permanent damage to mammals. The pharmaceutical compositions of the present invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the selected carrier material. Where appropriate, the other additives such as surface-active agents are prepared by micronisation, for instance
30 in view to obtain them in the form of microspheres usually having a diameter of

about 1 to 10 gm, namely for the manufacture of microcapsules for controlled or sustained release of the active ingredients.

Suitable surface-active agents, also known as emulgent or emulsifier, to be used in the pharmaceutical compositions of the present invention are non-ionic, cationic and/or anionic materials having good emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C_{10} - C_{22}), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable from coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alcoholamine salts of dodecylbenzene sulphonic acid or dibutyl-naphthalenesulphonic acid or a naphthalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphosphatidyl -choline and their mixtures.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol - polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C_8 - C_{22} alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Corp., Ridgewood, New Jersey, 1981), "Tensid-Taschenbuch", 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants, (Chemical Publishing Co., New York, 1981).

Compounds of the invention and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and
5 parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations,
10 both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically acceptable carriers therefore and optionally other. therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to
15 the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of
20 pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

25 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active
30 ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of the eye or other external tissues e.g. mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying

wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is

administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more

compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral
5 administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for
10 example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid,
15 hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectable use
20 include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

In view of the fact that, when several active ingredients are used in
25 combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way
30 suitable for an administration route different from that of the other ingredient,

e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Suitable methods for drug delivery include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

Several active ingredients used in combination may not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated. Thus, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Exemplary Enumerated Compounds

By way of example and not limitation, embodiments of the invention are named below in tabular format (Table 7). Each embodiment of Table 7 is depicted as a substituted nucleus (Sc) in which the nucleus is designated by a number and each substituent is designated in order by further numbers. Table 1 is a schedule of nuclei used in forming the embodiments of Table 7. Each nucleus (Sc) is given a number designation from Table 1, and this designation appears first in each embodiment name. Similarly, Tables 2, 3, 4, 5 and 6 list the selected substituents, again by number designation.

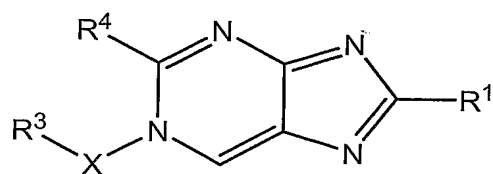
Accordingly, each named embodiment of Table 7 is depicted by a number designating the nucleus from Table 1. If the nucleus is of formula 1 (from Table

1), then the letter and number substituents are in the order R^1 (Table 2), R^3 (Table 3), R^4 (Table 4), and X (Table 6). If the nucleus is of formula 2 (from Table 1), then the letter and number substituents are in the order R^1 (Table 2), R^3 (Table 3), 4 (Table 4), R^{26} (Table 5), and X (Table 6). The same embodiments of the invention
5 exist for the nucleus of formula 2 (Table 1) wherein the N at position 1 is substituted by R^{25} (corresponding to the embodiments of R^{26} of Table 5) and the single or double bonds in the imidazo pyridine ring are adjusted accordingly.

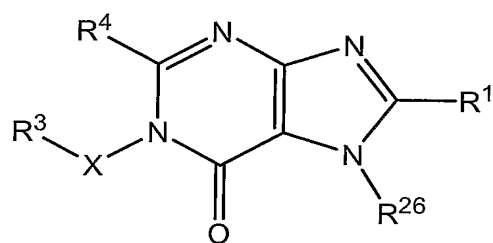
Each group is shown having one or more tildas ("~"). The tildas are the points of covalent attachment of the group.

Table 1

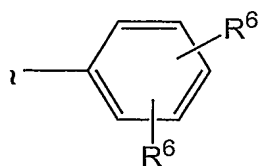
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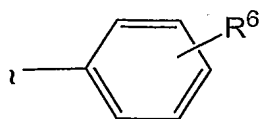
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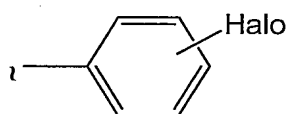
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Table 2 – R¹ Substituents

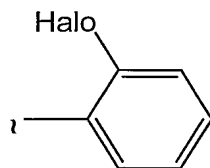
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2



3



4

I — 5-membered benzoannellated ring having 1-2 nitrogen atoms and 1-2 R⁶ groups

5

I — 6-membered benzoannellated ring having 1-2 nitrogen atoms and 1-2 R⁶ groups

6

I — naphthyl having 1-2 R⁶ groups

7

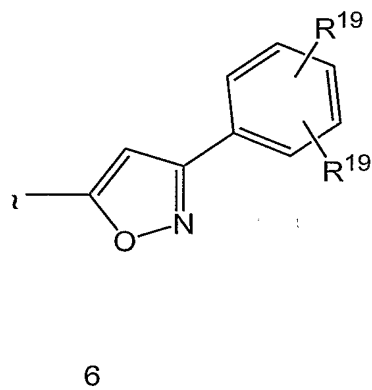
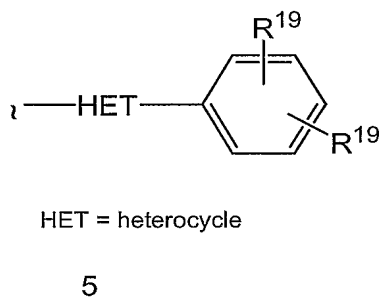
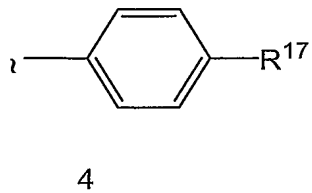
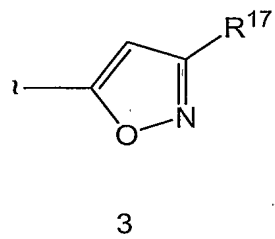
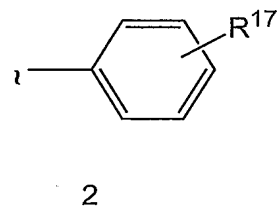
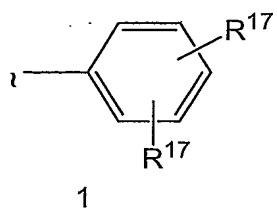
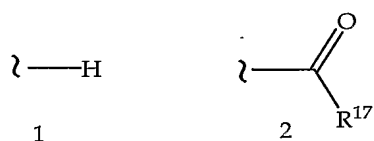
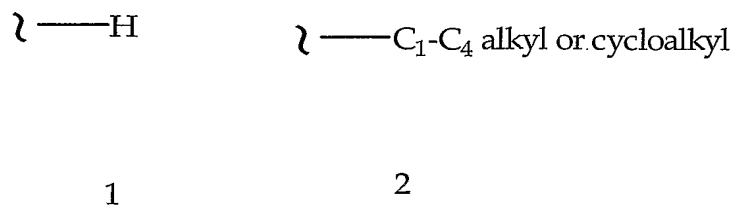
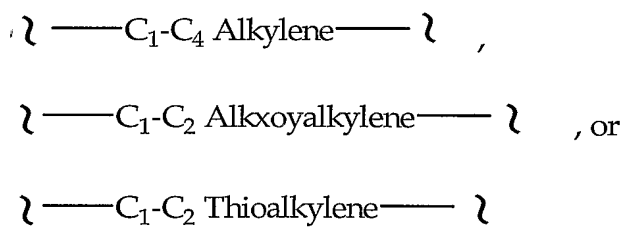
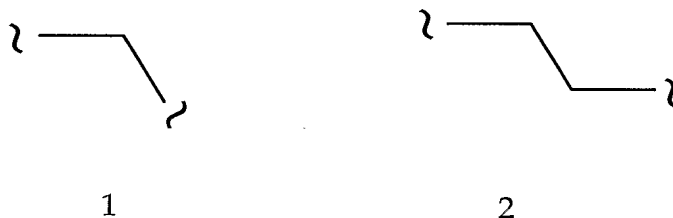
Table 3 – R³ Substituents

Table 4 – R⁴ SubstituentsTable 5 – R²⁶ Substituents

5

Table 6 – X Substituents

10

3

Table 7 – Selected Embodiments of the InventionEmbodiments of Formula 1

1.1.1.1.1; 1.1.1.1.2; 1.1.1.1.3; 1.1.1.2.1; 1.1.1.2.2; 1.1.1.2.3; 1.1.2.1.1; 1.1.2.1.2; 1.1.2.1.3;
 5 1.1.2.2.1; 1.1.2.2.2; 1.1.2.2.3; 1.1.3.1.1; 1.1.3.1.2; 1.1.3.1.3; 1.1.3.2.1; 1.1.3.2.2; 1.1.3.2.3;
 1.1.4.1.1; 1.1.4.1.2; 1.1.4.1.3; 1.1.4.2.1; 1.1.4.2.2; 1.1.4.2.3; 1.1.5.1.1; 1.1.5.1.2; 1.1.5.1.3;
 1.1.5.2.1; 1.1.5.2.2; 1.1.5.2.3; 1.1.6.1.1; 1.1.6.1.2; 1.1.6.1.3; 1.1.6.2.1; 1.1.6.2.2; 1.1.6.2.3;
 1.2.1.1.1; 1.2.1.1.2; 1.2.1.1.3; 1.2.1.2.1; 1.2.1.2.2; 1.2.1.2.3; 1.2.2.1.1; 1.2.2.1.2; 1.2.2.1.3;
 1.2.2.2.1; 1.2.2.2.2; 1.2.2.2.3; 1.2.3.1.1; 1.2.3.1.2; 1.2.3.1.3; 1.2.3.2.1; 1.2.3.2.2; 1.2.3.2.3;
 10 1.2.4.1.1; 1.2.4.1.2; 1.2.4.1.3; 1.2.4.2.1; 1.2.4.2.2; 1.2.4.2.3; 1.2.5.1.1; 1.2.5.1.2; 1.2.5.1.3;
 1.2.5.2.1; 1.2.5.2.2; 1.2.5.2.3; 1.2.6.1.1; 1.2.6.1.2; 1.2.6.1.3; 1.2.6.2.1; 1.2.6.2.2; 1.2.6.2.3;
 1.3.1.1.1; 1.3.1.1.2; 1.3.1.1.3; 1.3.1.2.1; 1.3.1.2.2; 1.3.1.2.3; 1.3.2.1.1; 1.3.2.1.2; 1.3.2.1.3;
 1.3.2.2.1; 1.3.2.2.2; 1.3.2.2.3; 1.3.3.1.1; 1.3.3.1.2; 1.3.3.1.3; 1.3.3.2.1; 1.3.3.2.2; 1.3.3.2.3;
 1.3.4.1.1; 1.3.4.1.2; 1.3.4.1.3; 1.3.4.2.1; 1.3.4.2.2; 1.3.4.2.3; 1.3.5.1.1; 1.3.5.1.2; 1.3.5.1.3;
 15 1.3.5.2.1; 1.3.5.2.2; 1.3.5.2.3; 1.3.6.1.1; 1.3.6.1.2; 1.3.6.1.3; 1.3.6.2.1; 1.3.6.2.2; 1.3.6.2.3;
 1.4.1.1.1; 1.4.1.1.2; 1.4.1.1.3; 1.4.1.2.1; 1.4.1.2.2; 1.4.1.2.3; 1.4.2.1.1; 1.4.2.1.2; 1.4.2.1.3;
 1.4.2.2.1; 1.4.2.2.2; 1.4.2.2.3; 1.4.3.1.1; 1.4.3.1.2; 1.4.3.1.3; 1.4.3.2.1; 1.4.3.2.2; 1.4.3.2.3;
 1.4.4.1.1; 1.4.4.1.2; 1.4.4.1.3; 1.4.4.2.1; 1.4.4.2.2; 1.4.4.2.3; 1.4.5.1.1; 1.4.5.1.2; 1.4.5.1.3;
 1.4.5.2.1; 1.4.5.2.2; 1.4.5.2.3; 1.4.6.1.1; 1.4.6.1.2; 1.4.6.1.3; 1.4.6.2.1; 1.4.6.2.2; 1.4.6.2.3;
 20 1.5.1.1.1; 1.5.1.1.2; 1.5.1.1.3; 1.5.1.2.1; 1.5.1.2.2; 1.5.1.2.3; 1.5.2.1.1; 1.5.2.1.2; 1.5.2.1.3;
 1.5.2.2.1; 1.5.2.2.2; 1.5.2.2.3; 1.5.3.1.1; 1.5.3.1.2; 1.5.3.1.3; 1.5.3.2.1; 1.5.3.2.2; 1.5.3.2.3;
 1.5.4.1.1; 1.5.4.1.2; 1.5.4.1.3; 1.5.4.2.1; 1.5.4.2.2; 1.5.4.2.3; 1.5.5.1.1; 1.5.5.1.2; 1.5.5.1.3;
 1.5.5.2.1; 1.5.5.2.2; 1.5.5.2.3; 1.5.6.1.1; 1.5.6.1.2; 1.5.6.1.3; 1.5.6.2.1; 1.5.6.2.2; 1.5.6.2.3;
 1.6.1.1.1; 1.6.1.1.2; 1.6.1.1.3; 1.6.1.2.1; 1.6.1.2.2; 1.6.1.2.3; 1.6.2.1.1; 1.6.2.1.2; 1.6.2.1.3;
 25 1.6.2.2.1; 1.6.2.2.2; 1.6.2.2.3; 1.6.3.1.1; 1.6.3.1.2; 1.6.3.1.3; 1.6.3.2.1; 1.6.3.2.2; 1.6.3.2.3;
 1.6.4.1.1; 1.6.4.1.2; 1.6.4.1.3; 1.6.4.2.1; 1.6.4.2.2; 1.6.4.2.3; 1.6.5.1.1; 1.6.5.1.2; 1.6.5.1.3;
 1.6.5.2.1; 1.6.5.2.2; 1.6.5.2.3; 1.6.6.1.1; 1.6.6.1.2; 1.6.6.1.3; 1.6.6.2.1; 1.6.6.2.2; 1.6.6.2.3;
 1.7.1.1.1; 1.7.1.1.2; 1.7.1.1.3; 1.7.1.2.1; 1.7.1.2.2; 1.7.1.2.3; 1.7.2.1.1; 1.7.2.1.2; 1.7.2.1.3;
 1.7.2.2.1; 1.7.2.2.2; 1.7.2.2.3; 1.7.3.1.1; 1.7.3.1.2; 1.7.3.1.3; 1.7.3.2.1; 1.7.3.2.2; 1.7.3.2.3;
 30 1.7.4.1.1; 1.7.4.1.2; 1.7.4.1.3; 1.7.4.2.1; 1.7.4.2.2; 1.7.4.2.3; 1.7.5.1.1; 1.7.5.1.2; 1.7.5.1.3;
 1.7.5.2.1; 1.7.5.2.2; 1.7.5.2.3; 1.7.6.1.1; 1.7.6.1.2; 1.7.6.1.3; 1.7.6.2.1; 1.7.6.2.2; 1.7.6.2.3.

Embodiments of Formula 2

35 2.1.1.1.1.1; 2.1.1.1.1.2; 2.1.1.1.1.3; 2.1.1.1.2.1; 2.1.1.1.2.2; 2.1.1.1.2.3; 2.1.1.2.1.1;
 2.1.1.2.1.2; 2.1.1.2.1.3; 2.1.1.2.2.1; 2.1.1.2.2.2; 2.1.1.2.2.3; 2.1.2.1.1.1; 2.1.2.1.1.2;
 2.1.2.1.1.3; 2.1.2.1.2.1; 2.1.2.1.2.2; 2.1.2.1.2.3; 2.1.2.2.1.1; 2.1.2.2.1.2; 2.1.2.2.1.3;
 2.1.2.2.2.1; 2.1.2.2.2.2; 2.1.2.2.2.3; 2.1.3.1.1.1; 2.1.3.1.1.2; 2.1.3.1.1.3; 2.1.3.1.2.1;
 2.1.3.1.2.2; 2.1.3.1.2.3; 2.1.3.2.1.1; 2.1.3.2.1.2; 2.1.3.2.1.3; 2.1.3.2.2.1; 2.1.3.2.2.2;
 40 2.1.3.2.2.3; 2.1.4.1.1.1; 2.1.4.1.1.2; 2.1.4.1.1.3; 2.1.4.1.2.1; 2.1.4.1.2.2; 2.1.4.1.2.3;
 2.1.4.2.1.1; 2.1.4.2.1.2; 2.1.4.2.1.3; 2.1.4.2.2.1; 2.1.4.2.2.2; 2.1.4.2.2.3; 2.1.5.1.1.1;
 2.1.5.1.1.2; 2.1.5.1.1.3; 2.1.5.1.2.1; 2.1.5.1.2.2; 2.1.5.1.2.3; 2.1.5.2.1.1; 2.1.5.2.1.2;
 2.1.5.2.1.3; 2.1.5.2.2.1; 2.1.5.2.2.2; 2.1.5.2.2.3; 2.1.6.1.1.1; 2.1.6.1.1.2; 2.1.6.1.1.3;
 2.1.6.1.2.1; 2.1.6.1.2.2; 2.1.6.1.2.3; 2.1.6.2.1.1; 2.1.6.2.1.2; 2.1.6.2.1.3; 2.1.6.2.2.1;
 45 2.1.6.2.2.2; 2.1.6.2.2.3; 2.2.1.1.1.1; 2.2.1.1.1.2; 2.2.1.1.1.3; 2.2.1.1.2.1; 2.2.1.1.2.2;
 2.2.1.1.2.3; 2.2.1.2.1.1; 2.2.1.2.1.2; 2.2.1.2.1.3; 2.2.1.2.2.1; 2.2.1.2.2.2; 2.2.1.2.2.3;

	2.2.2.1.1.1; 2.2.2.1.1.2; 2.2.2.1.1.3; 2.2.2.1.2.1; 2.2.2.1.2.2; 2.2.2.1.2.3; 2.2.2.2.1.1;
	2.2.2.2.1.2; 2.2.2.2.1.3; 2.2.2.2.2.1; 2.2.2.2.2.2; 2.2.2.2.2.3; 2.2.3.1.1.1; 2.2.3.1.1.2;
	2.2.3.1.1.3; 2.2.3.1.2.1; 2.2.3.1.2.2; 2.2.3.1.2.3; 2.2.3.2.1.1; 2.2.3.2.1.2; 2.2.3.2.1.3;
	2.2.3.2.2.1; 2.2.3.2.2.2; 2.2.3.2.2.3; 2.2.4.1.1.1; 2.2.4.1.1.2; 2.2.4.1.1.3; 2.2.4.1.2.1;
5	2.2.4.1.2.2; 2.2.4.1.2.3; 2.2.4.2.1.1; 2.2.4.2.1.2; 2.2.4.2.1.3; 2.2.4.2.2.1; 2.2.4.2.2.2;
	2.2.4.2.2.3; 2.2.5.1.1.1; 2.2.5.1.1.2; 2.2.5.1.1.3; 2.2.5.1.2.1; 2.2.5.1.2.2; 2.2.5.1.2.3;
	2.2.5.2.1.1; 2.2.5.2.1.2; 2.2.5.2.1.3; 2.2.5.2.2.1; 2.2.5.2.2.2; 2.2.5.2.2.3; 2.2.6.1.1.1;
	2.2.6.1.1.2; 2.2.6.1.1.3; 2.2.6.1.2.1; 2.2.6.1.2.2; 2.2.6.1.2.3; 2.2.6.2.1.1; 2.2.6.2.1.2;
	2.2.6.2.1.3; 2.2.6.2.2.1; 2.2.6.2.2.2; 2.2.6.2.2.3; 2.3.1.1.1.1; 2.3.1.1.1.2; 2.3.1.1.1.3;
10	2.3.1.1.2.1; 2.3.1.1.2.2; 2.3.1.1.2.3; 2.3.1.2.1.1; 2.3.1.2.1.2; 2.3.1.2.1.3; 2.3.1.2.2.1;
	2.3.1.2.2.2; 2.3.1.2.2.3; 2.3.2.1.1.1; 2.3.2.1.1.2; 2.3.2.1.1.3; 2.3.2.1.2.1; 2.3.2.1.2.2;
	2.3.2.1.2.3; 2.3.2.2.1.1; 2.3.2.2.1.2; 2.3.2.2.1.3; 2.3.2.2.2.1; 2.3.2.2.2.2; 2.3.2.2.2.3;
	2.3.3.1.1.1; 2.3.3.1.1.2; 2.3.3.1.1.3; 2.3.3.1.2.1; 2.3.3.1.2.2; 2.3.3.1.2.3; 2.3.3.2.1.1;
	2.3.3.2.1.2; 2.3.3.2.1.3; 2.3.3.2.2.1; 2.3.3.2.2.2; 2.3.3.2.2.3; 2.3.4.1.1.1; 2.3.4.1.1.2;
15	2.3.4.1.1.3; 2.3.4.1.2.1; 2.3.4.1.2.2; 2.3.4.1.2.3; 2.3.4.2.1.1; 2.3.4.2.1.2; 2.3.4.2.1.3;
	2.3.4.2.2.1; 2.3.4.2.2.2; 2.3.4.2.2.3; 2.3.5.1.1.1; 2.3.5.1.1.2; 2.3.5.1.1.3; 2.3.5.1.2.1;
	2.3.5.1.2.2; 2.3.5.1.2.3; 2.3.5.2.1.1; 2.3.5.2.1.2; 2.3.5.2.1.3; 2.3.5.2.2.1; 2.3.5.2.2.2;
	2.3.5.2.2.3; 2.3.6.1.1.1; 2.3.6.1.1.2; 2.3.6.1.1.3; 2.3.6.1.2.1; 2.3.6.1.2.2; 2.3.6.1.2.3;
	2.3.6.2.1.1; 2.3.6.2.1.2; 2.3.6.2.1.3; 2.3.6.2.2.1; 2.3.6.2.2.2; 2.3.6.2.2.3; 2.4.1.1.1.1;
20	2.4.1.1.1.2; 2.4.1.1.1.3; 2.4.1.1.2.1; 2.4.1.1.2.2; 2.4.1.1.2.3; 2.4.1.2.1.1; 2.4.1.2.1.2;
	2.4.1.2.1.3; 2.4.1.2.2.1; 2.4.1.2.2.2; 2.4.1.2.2.3; 2.4.2.1.1.1; 2.4.2.1.1.2; 2.4.2.1.1.3;
	2.4.2.1.2.1; 2.4.2.1.2.2; 2.4.2.1.2.3; 2.4.2.2.1.1; 2.4.2.2.1.2; 2.4.2.2.1.3; 2.4.2.2.2.1;
	2.4.2.2.2.2; 2.4.2.2.2.3; 2.4.3.1.1.1; 2.4.3.1.1.2; 2.4.3.1.1.3; 2.4.3.1.2.1; 2.4.3.1.2.2;
	2.4.3.1.2.3; 2.4.3.2.1.1; 2.4.3.2.1.2; 2.4.3.2.1.3; 2.4.3.2.2.1; 2.4.3.2.2.2; 2.4.3.2.2.3;
25	2.4.4.1.1.1; 2.4.4.1.1.2; 2.4.4.1.1.3; 2.4.4.1.2.1; 2.4.4.1.2.2; 2.4.4.1.2.3; 2.4.4.2.1.1;
	2.4.4.2.1.2; 2.4.4.2.1.3; 2.4.4.2.2.1; 2.4.4.2.2.2; 2.4.4.2.2.3; 2.4.5.1.1.1; 2.4.5.1.1.2;
	2.4.5.1.1.3; 2.4.5.1.2.1; 2.4.5.1.2.2; 2.4.5.1.2.3; 2.4.5.2.1.1; 2.4.5.2.1.2; 2.4.5.2.1.3;
	2.4.5.2.2.1; 2.4.5.2.2.2; 2.4.5.2.2.3; 2.4.6.1.1.1; 2.4.6.1.1.2; 2.4.6.1.1.3; 2.4.6.1.2.1;
	2.4.6.1.2.2; 2.4.6.1.2.3; 2.4.6.2.1.1; 2.4.6.2.1.2; 2.4.6.2.1.3; 2.4.6.2.2.1; 2.4.6.2.2.2;
30	2.4.6.2.2.3; 2.5.1.1.1.1; 2.5.1.1.1.2; 2.5.1.1.1.3; 2.5.1.1.2.1; 2.5.1.1.2.2; 2.5.1.1.2.3;
	2.5.1.2.1.1; 2.5.1.2.1.2; 2.5.1.2.1.3; 2.5.1.2.2.1; 2.5.1.2.2.2; 2.5.1.2.2.3; 2.5.2.1.1.1;
	2.5.2.1.1.2; 2.5.2.1.1.3; 2.5.2.1.2.1; 2.5.2.1.2.2; 2.5.2.1.2.3; 2.5.2.2.1.1; 2.5.2.2.1.2;
	2.5.2.2.1.3; 2.5.2.2.2.1; 2.5.2.2.2.2; 2.5.2.2.2.3; 2.5.3.1.1.1; 2.5.3.1.1.2; 2.5.3.1.1.3;
	2.5.3.1.2.1; 2.5.3.1.2.2; 2.5.3.1.2.3; 2.5.3.2.1.1; 2.5.3.2.1.2; 2.5.3.2.1.3; 2.5.3.2.2.1;
35	2.5.3.2.2.2; 2.5.3.2.2.3; 2.5.4.1.1.1; 2.5.4.1.1.2; 2.5.4.1.1.3; 2.5.4.1.2.1; 2.5.4.1.2.2;
	2.5.4.1.2.3; 2.5.4.2.1.1; 2.5.4.2.1.2; 2.5.4.2.1.3; 2.5.4.2.2.1; 2.5.4.2.2.2; 2.5.4.2.2.3;
	2.5.5.1.1.1; 2.5.5.1.1.2; 2.5.5.1.1.3; 2.5.5.1.2.1; 2.5.5.1.2.2; 2.5.5.1.2.3; 2.5.5.2.1.1;
	2.5.5.2.1.2; 2.5.5.2.1.3; 2.5.5.2.2.1; 2.5.5.2.2.2; 2.5.5.2.2.3; 2.5.6.1.1.1; 2.5.6.1.1.2;
	2.5.6.1.1.3; 2.5.6.1.2.1; 2.5.6.1.2.2; 2.5.6.1.2.3; 2.5.6.2.1.1; 2.5.6.2.1.2; 2.5.6.2.1.3;
40	2.5.6.2.2.1; 2.5.6.2.2.2; 2.5.6.2.2.3; 2.6.1.1.1.1; 2.6.1.1.1.2; 2.6.1.1.1.3; 2.6.

2.6.4.2.2.2; 2.6.4.2.2.3; 2.6.5.1.1.1; 2.6.5.1.1.2; 2.6.5.1.1.3; 2.6.5.1.2.1; 2.6.5.1.2.2;
2.6.5.1.2.3; 2.6.5.2.1.1; 2.6.5.2.1.2; 2.6.5.2.1.3; 2.6.5.2.2.1; 2.6.5.2.2.2; 2.6.5.2.2.3;
2.6.6.1.1.1; 2.6.6.1.1.2; 2.6.6.1.1.3; 2.6.6.1.2.1; 2.6.6.1.2.2; 2.6.6.1.2.3; 2.6.6.2.1.1;
2.6.6.2.1.2; 2.6.6.2.1.3; 2.6.6.2.2.1; 2.6.6.2.2.2; 2.6.6.2.2.3; 2.7.1.1.1.1; 2.7.1.1.1.2;
5 2.7.1.1.1.3; 2.7.1.1.2.1; 2.7.1.1.2.2; 2.7.1.1.2.3; 2.7.1.2.1.1; 2.7.1.2.1.2; 2.7.1.2.1.3;
2.7.1.2.2.1; 2.7.1.2.2.2; 2.7.1.2.2.3; 2.7.2.1.1.1; 2.7.2.1.1.2; 2.7.2.1.1.3; 2.7.2.1.2.1;
2.7.2.1.2.2; 2.7.2.1.2.3; 2.7.2.2.1.1; 2.7.2.2.1.2; 2.7.2.2.1.3; 2.7.2.2.2.1; 2.7.2.2.2.2;
2.7.2.2.2.3; 2.7.3.1.1.1; 2.7.3.1.1.2; 2.7.3.1.1.3; 2.7.3.1.2.1; 2.7.3.1.2.2; 2.7.3.1.2.3;
2.7.3.2.1.1; 2.7.3.2.1.2; 2.7.3.2.1.3; 2.7.3.2.2.1; 2.7.3.2.2.2; 2.7.3.2.2.3; 2.7.4.1.1.1;
10 2.7.4.1.1.2; 2.7.4.1.1.3; 2.7.4.1.2.1; 2.7.4.1.2.2; 2.7.4.1.2.3; 2.7.4.2.1.1; 2.7.4.2.1.2;
2.7.4.2.1.3; 2.7.4.2.2.1; 2.7.4.2.2.2; 2.7.4.2.2.3; 2.7.5.1.1.1; 2.7.5.1.1.2; 2.7.5.1.1.3;
2.7.5.1.2.1; 2.7.5.1.2.2; 2.7.5.1.2.3; 2.7.5.2.1.1; 2.7.5.2.1.2; 2.7.5.2.1.3; 2.7.5.2.2.1;
2.7.5.2.2.2; 2.7.5.2.2.3; 2.7.6.1.1.1; 2.7.6.1.1.2; 2.7.6.1.1.3; 2.7.6.1.2.1; 2.7.6.1.2.2;
15 2.7.6.1.2.3; 2.7.6.2.1.1; 2.7.6.2.1.2; 2.7.6.2.1.3; 2.7.6.2.2.1; 2.7.6.2.2.2; 2.7.6.2.2.3.

General methods and materials for the preparation of the compounds of the invention

Synthetic Methods

The compounds of the formulas of this invention are prepared using a series of chemical reactions well known to those skilled in the art, altogether
20 making up the process for preparing said compounds and exemplified further. The processes described further are only meant as examples and by no means are meant to limit the scope of the present invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of
25 organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr., 1980; Vol. 5,
30 Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

Exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations, and are not intended to limit the scope of applicable methods.

5 Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and
10 reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions
15 frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations
20 reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments)
25 are common in the art and will be applied when applicable.

General aspects of these exemplary methods are described below. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The terms "treated", "treating", "treatment", and the like, mean contacting,
30 mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in

such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other
5 expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically
10 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar
15 reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

20 Modification of the exemplified schemes and examples leads to various analogs of the specific exemplary materials produced above. The above citations describing suitable methods of organic synthesis are applicable to such modifications.

In the exemplary schemes it may be advantageous to separate reaction
25 products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art.

Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography.

30 Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid

chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. Such separations are desirable if addition reactions place substituents at both of the pyrimidine nitrogen atoms. Separation of these isomers is well within the skill of
5 the artisan.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion
10 exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

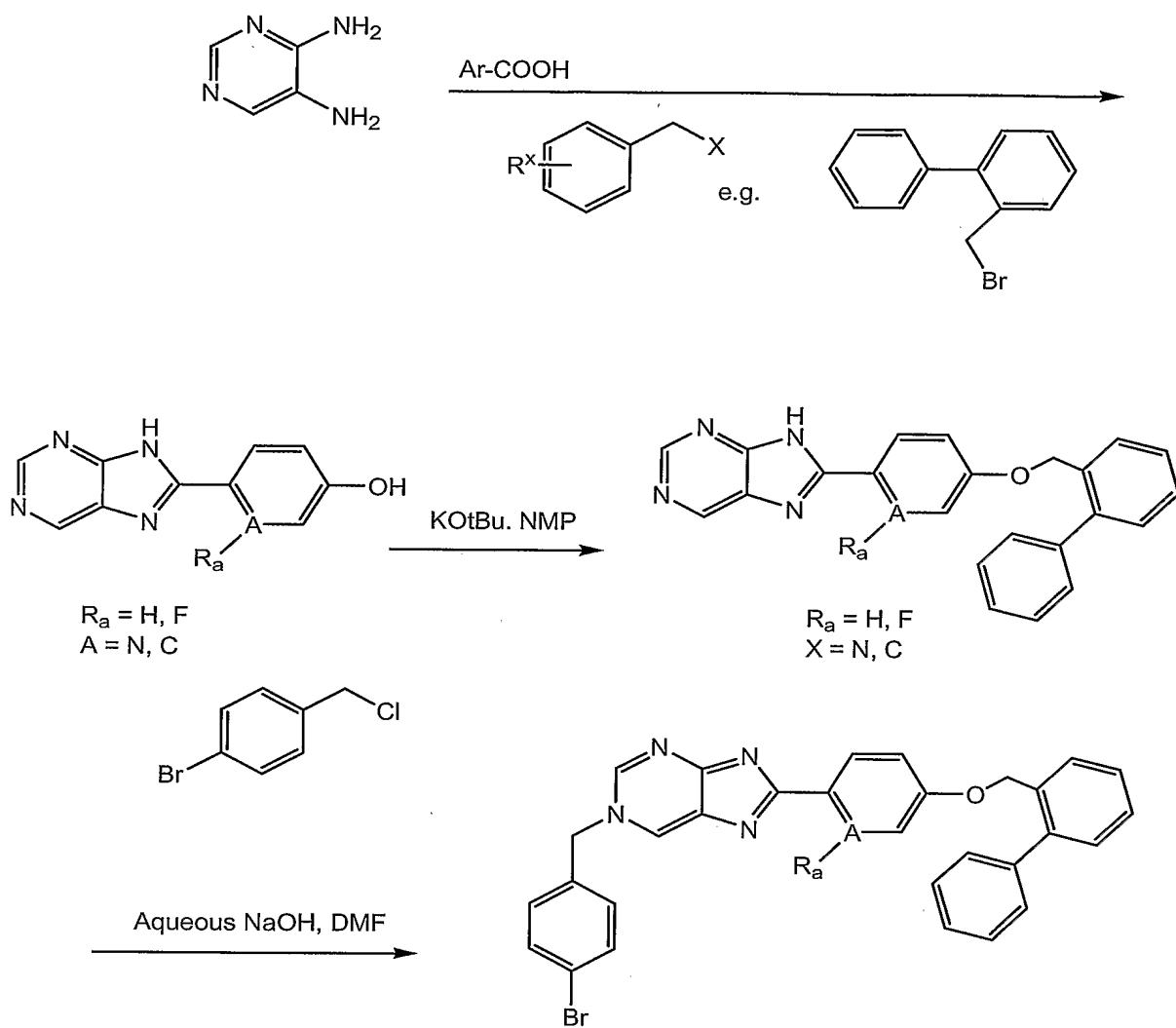
Selection of appropriate methods of separation depends on the nature of
15 the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

20 A synthetic route to 5-benzyl-2-phenyl-5H-imidazo[4,5-d]pyrimidine and analogues is shown in Scheme A.

25

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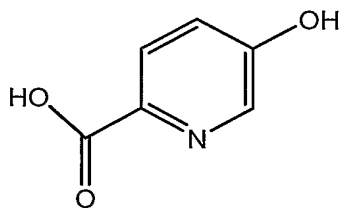
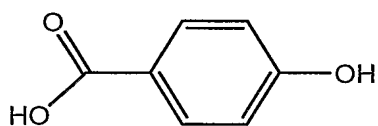
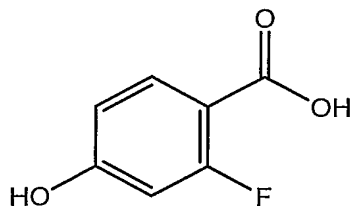
Scheme A:



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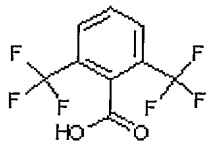
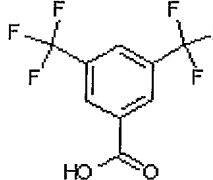
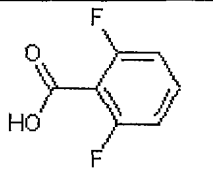
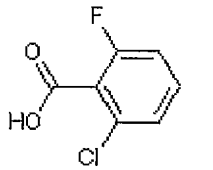
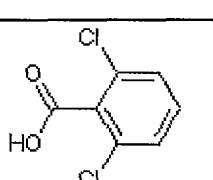
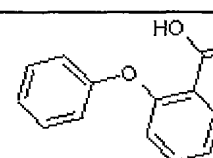
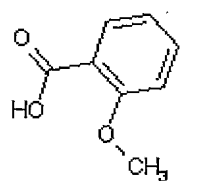
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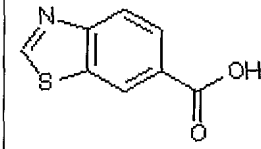
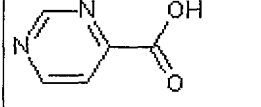
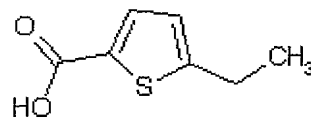
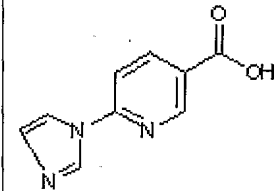
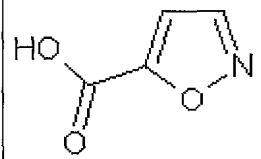
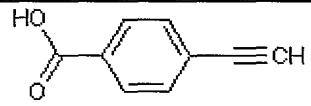
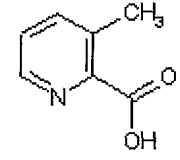
Exemplary Ar COOH reactants are

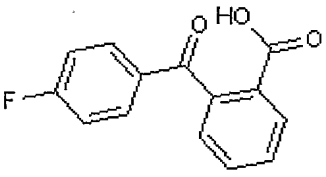
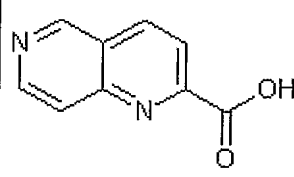
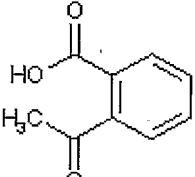
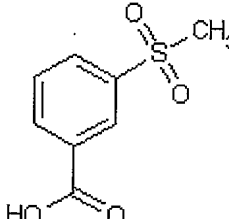
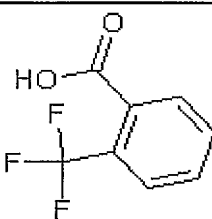
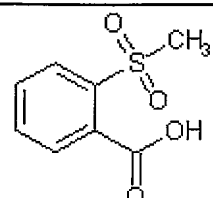
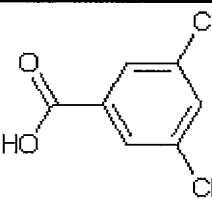
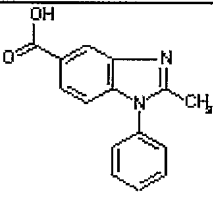
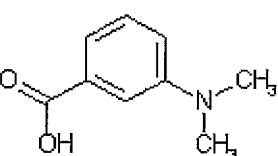
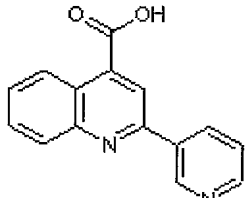
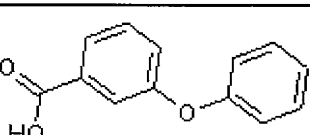
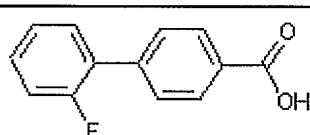

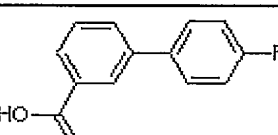
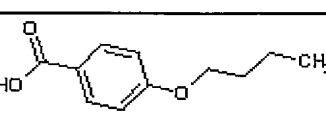
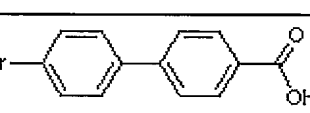


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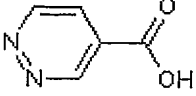
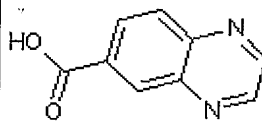
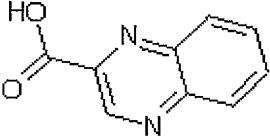
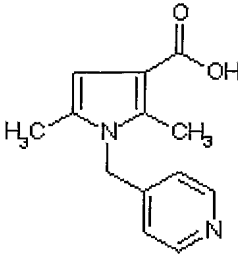
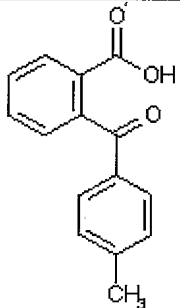
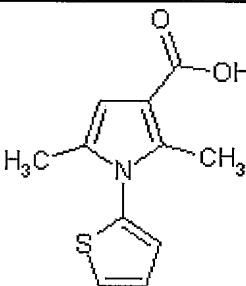
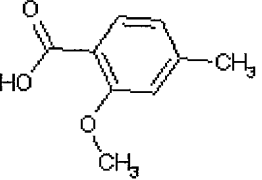
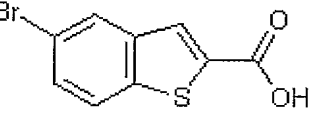

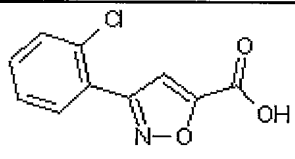
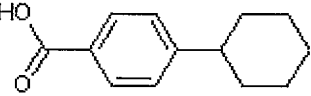
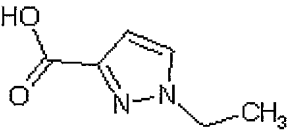
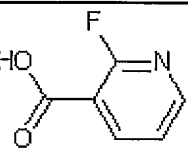
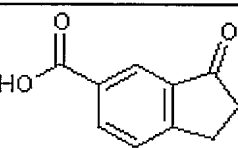
The following list includes additional carboxylic acid reactants which may
10 be employed in the condensation, ring closure reaction of Scheme A. The
compounds so produced will bear the residue of the acid at the site of YR¹.
Optionally, the remainder of the molecule will be for example as in any of the
compounds exemplified below.

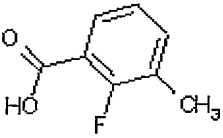
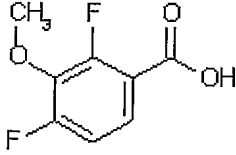
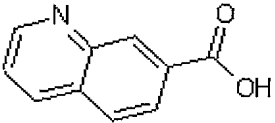
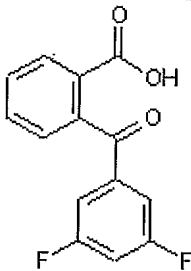
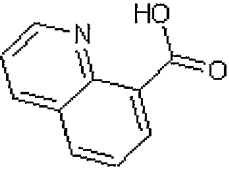
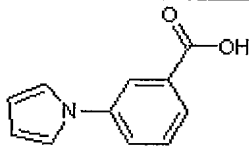
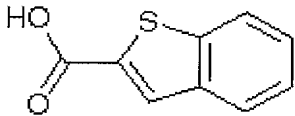
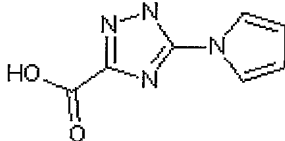
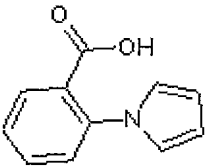
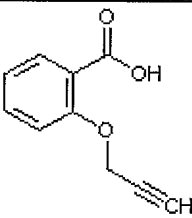
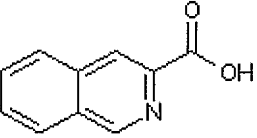
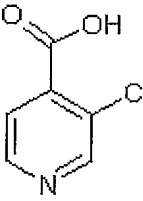
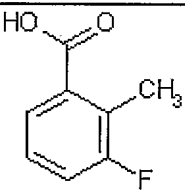
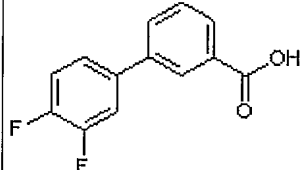
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	258.117
	158.103
	174.558
	191.013
	214.219
	152.148

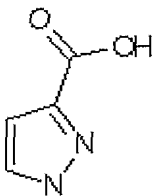
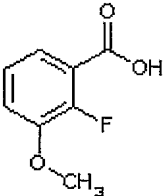
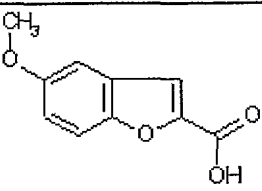
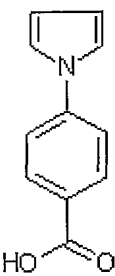
Acid	MW
	179.199
	124.099
	156.204
	189.173
	113.072
	146.144
	137.137

	244.22		174.158
	164.159		200.213
	190.12		200.213
	191.013		252.272
	165.191		250.256
	214.219		216.21
	206.118		216.21
	194.229		277.116

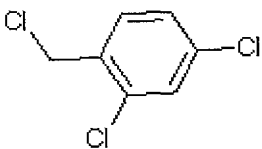
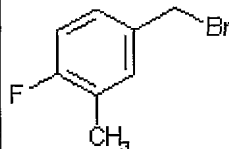
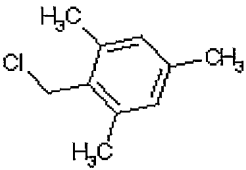
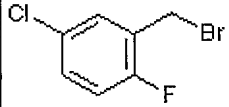
	164.159		215.251
	178.23		215.251
	125.126		126.114
	112.084		129.139
	128.151		143.165
	124.099		124.099
	200.213		127.099
	201.201		126.114
	112.088		222.238

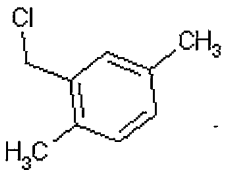
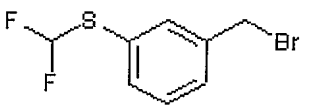
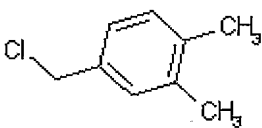
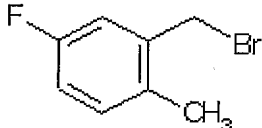
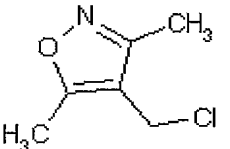
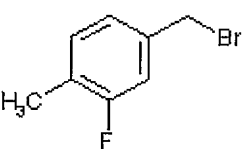
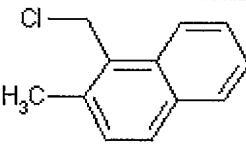
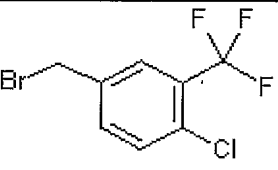
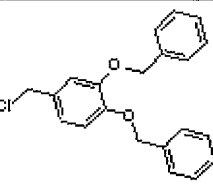
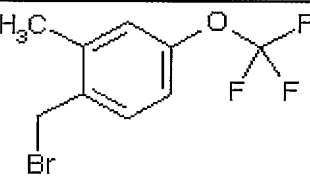
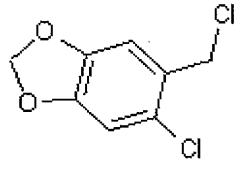
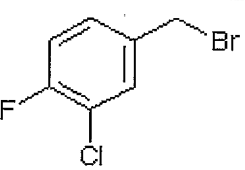
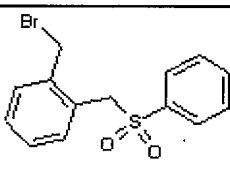
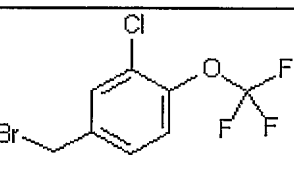
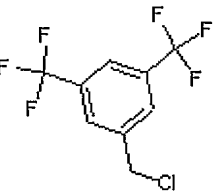
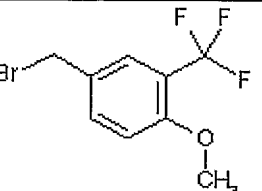
	124.099		174.158
	174.158		230.266
	240.257		221.279
	166.175		257.107
	137.137		223.614
	204.267		140.141
	141.101		176.17

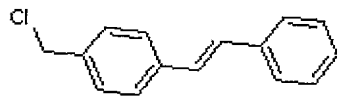
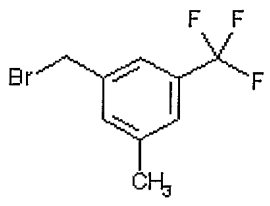
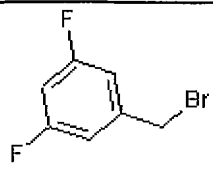
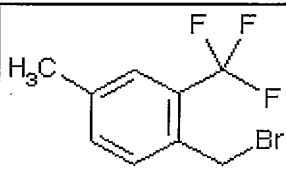
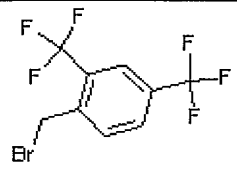
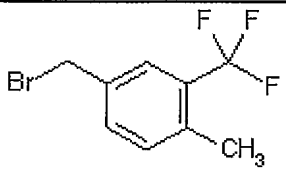
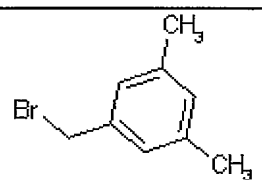
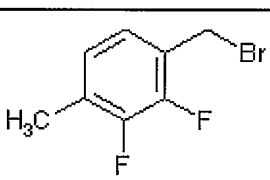
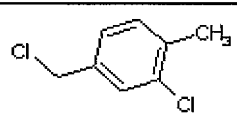
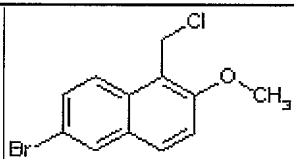

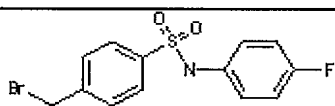
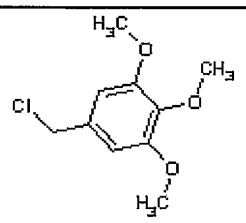
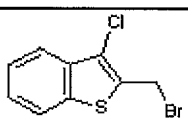
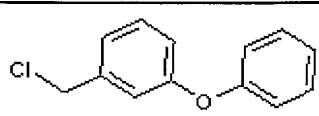
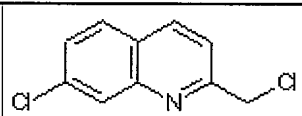
	154.139		188.128
	173.17		262.21
	173.17		187.197
	178.21		178.15
	187.197		176.17
	173.17		157.556
	154.139		234.2

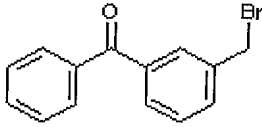
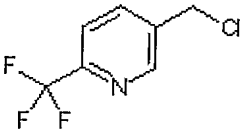
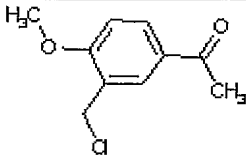
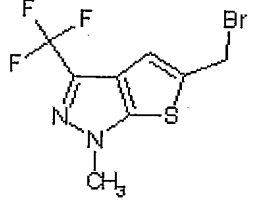
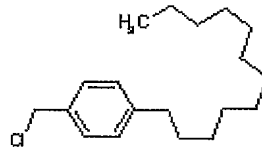
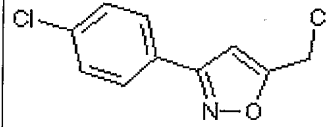
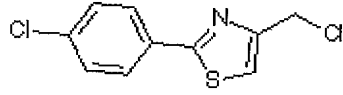
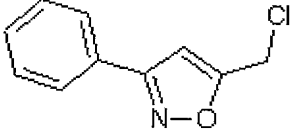
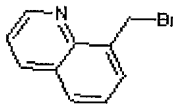
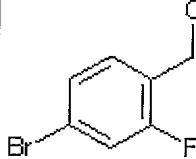

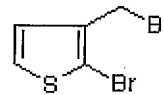
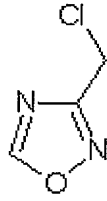
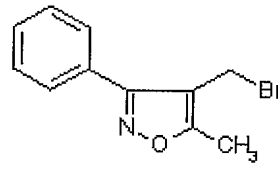
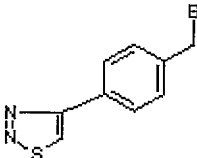
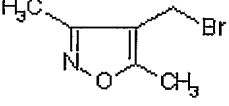
	112.088		170.138
	192.169		
	187.197		

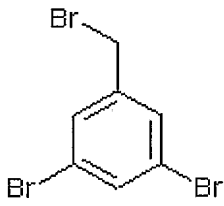
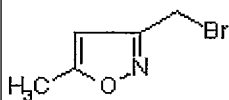
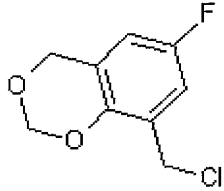
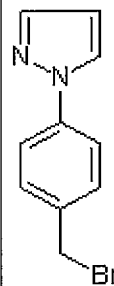
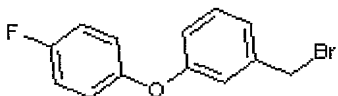
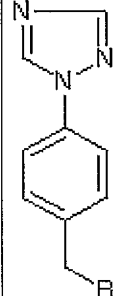
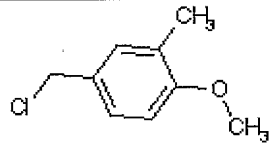
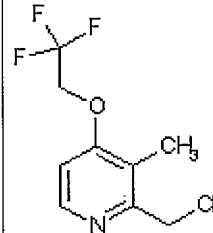
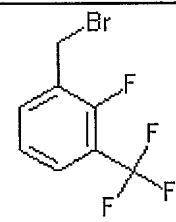
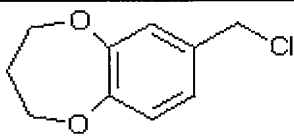
The following list includes alkylating reagents which may be employed in the pyridyl alkylation reaction of Scheme A. Here, the residue of the alkylating agent is located at the X R³ site of the compound of this invention. Optionally, the remainder of the compound will be as found in any of the compounds of examples.

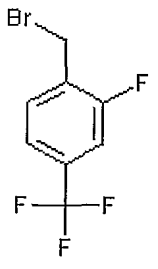
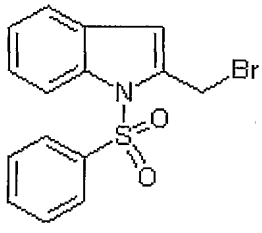
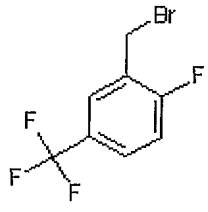
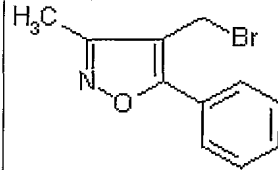
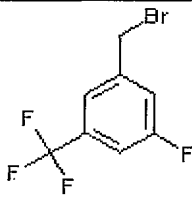
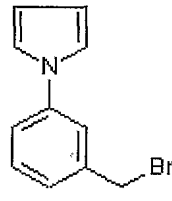
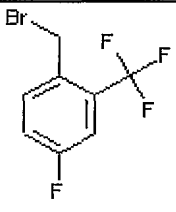
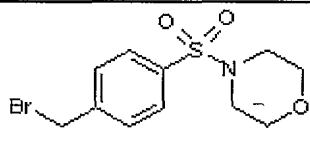
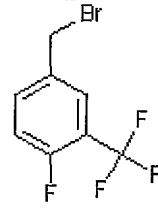
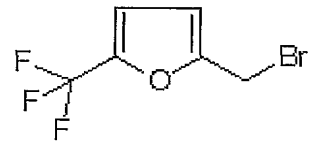
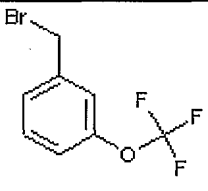
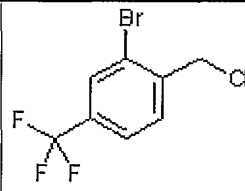
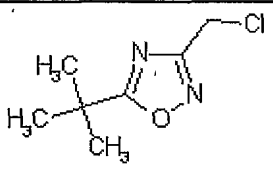
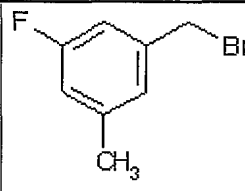
Alkylating reagent	MW	Alkylating reagent	MW
	195.475		203.053
	168.666		223.471

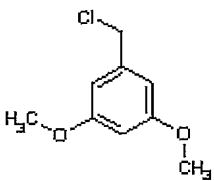
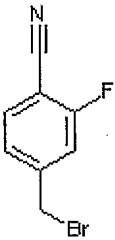
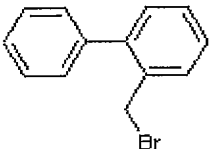
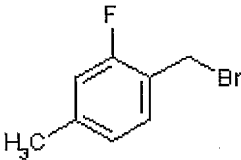
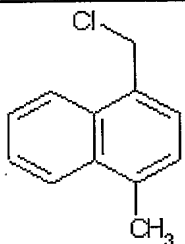
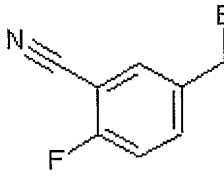
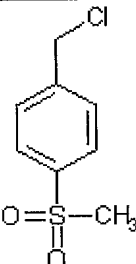
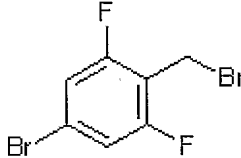
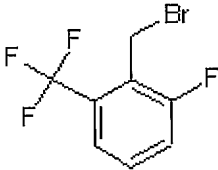
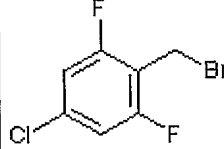
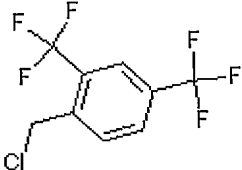
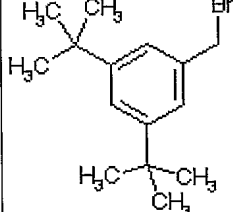
	154.639		253.109
	154.639		203.053
	145.588		203.053
	190.672		273.478
	338.832		269.059
	205.039		223.471
	325.225		289.478
	262.579		269.059

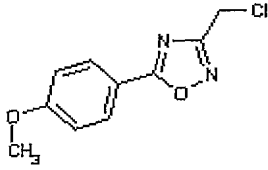
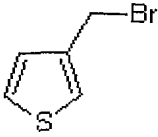
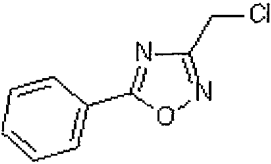
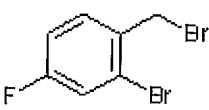
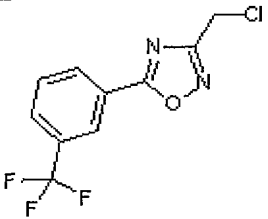
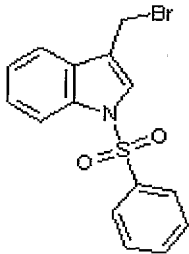
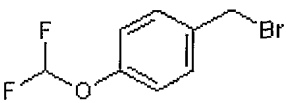
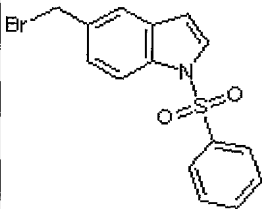
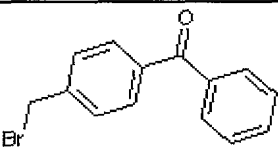
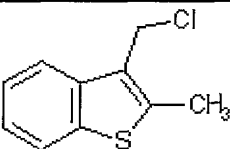
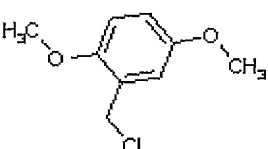
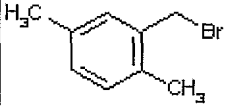
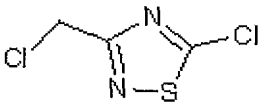
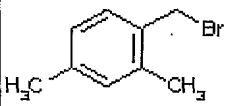
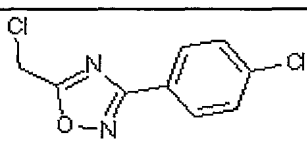
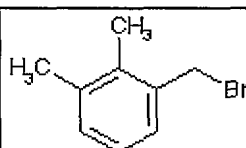
	228.721		253.06
	207.016		253.06
	307.03		253.06
	199.09		221.043
	175.057		285.567
	154.639		344.203
	216.663		261.569
	218.682		212.078

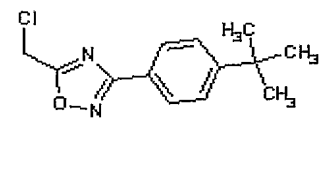
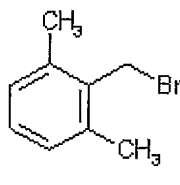
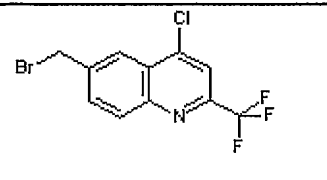
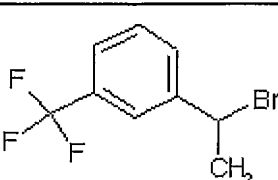
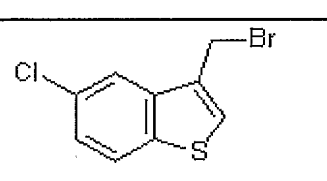
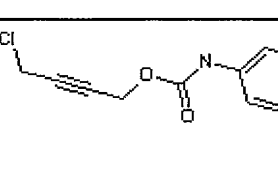
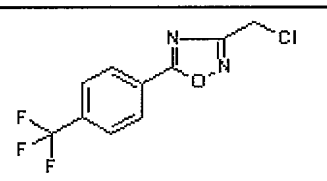
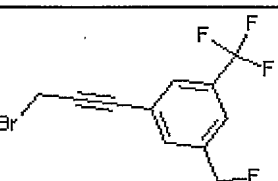
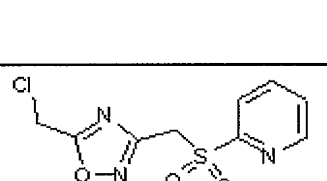
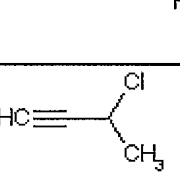
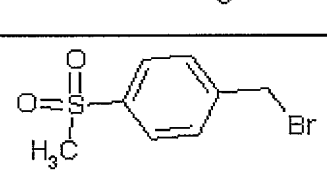
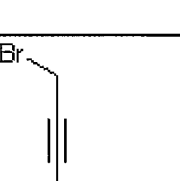
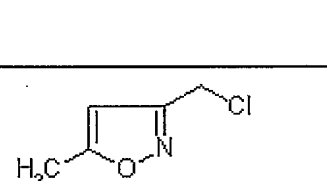
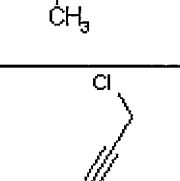
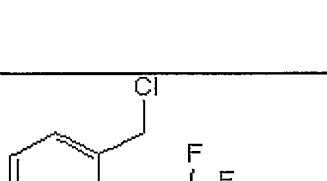
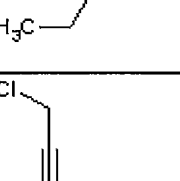
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	198.648		299.113
	294.907		228.077
	244.144		193.632
	222.084		223.471
	152.623		255.961
	118.523		252.11
	255.138		190.039

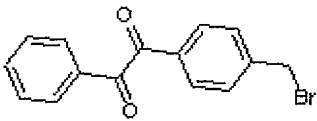
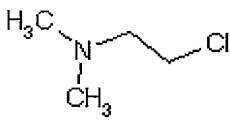
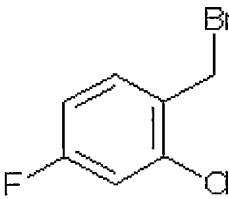
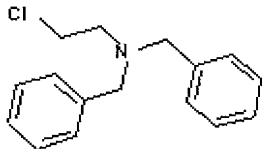
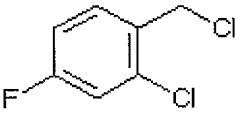
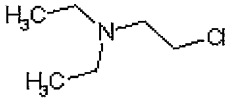
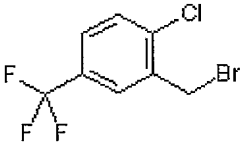
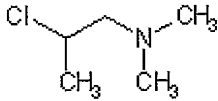
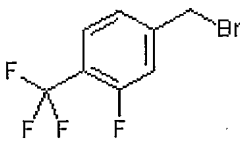

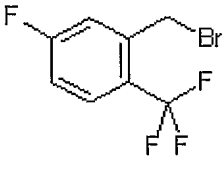

 <chem>BrCc1cc(Br)cc(Br)c1</chem>	328.828	 <chem>BrCc1cc(C)nn1</chem>	176.012
 <chem>ClCc1cc(F)ccc1OCCO</chem>	202.611	 <chem>BrCc1ccc(cc1)n2cc[nH]2</chem>	237.099
 <chem>BrCc1ccc(Oc2ccc(F)cc2)cc1</chem>	281.123	 <chem>BrCc1ccc(cc1)n2cc[nH]2</chem>	238.087
 <chem>COc1cc(CCl)ccc1C</chem>	170.638	 <chem>COc1cc(CCl)cc(C(F)(F)F)cn1</chem>	239.623
 <chem>BrCc1cc(F)c(C(F)(F)F)cc1</chem>	257.023	 <chem>ClCc1ccc2c(c1)OCCO2</chem>	198.648

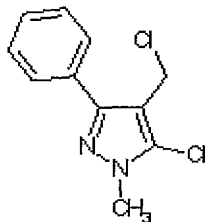
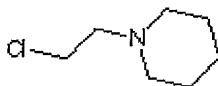
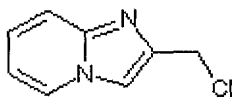
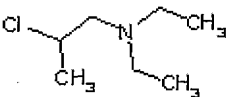
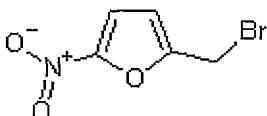
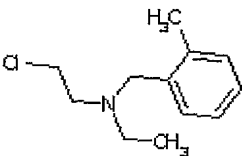
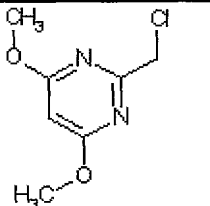
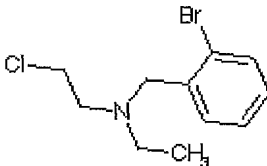
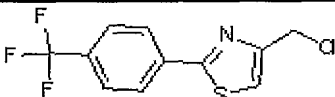
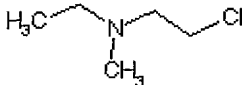
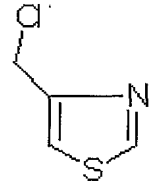
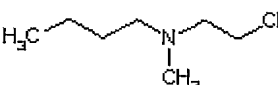
	257.023		350.235
	257.023		252.11
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	255.032		273.478
	174.63		203.053

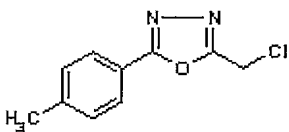
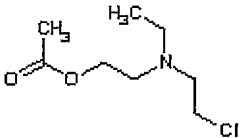
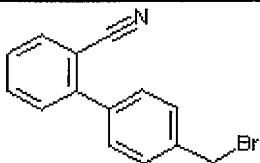
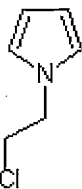
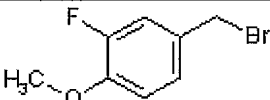
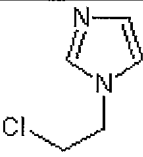
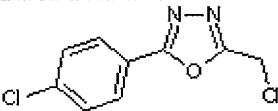
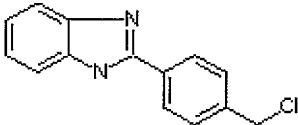
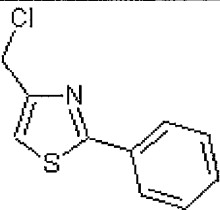
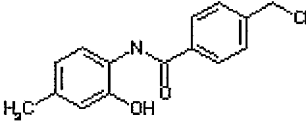
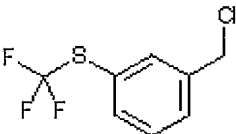
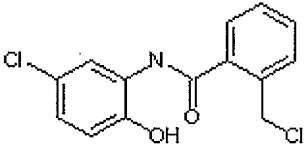
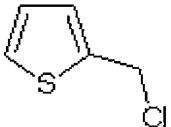
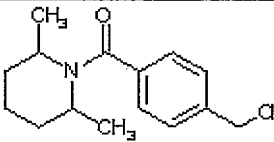
	186.637		214.036
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	190.672		214.036
	204.676		285.913
	257.023		241.462
	262.579		283.251

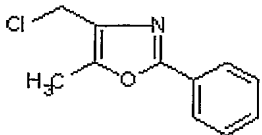
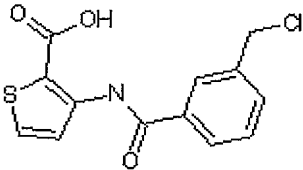
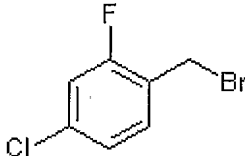
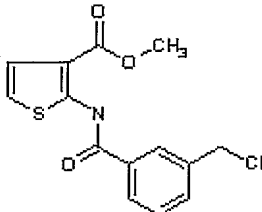
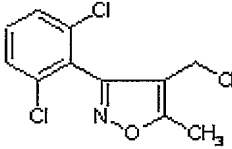
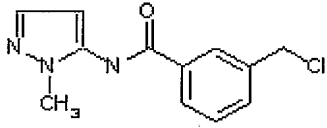
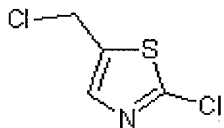
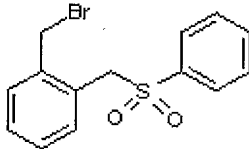
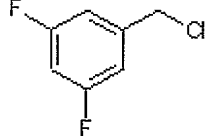
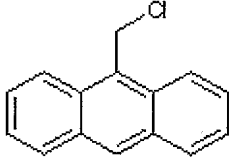
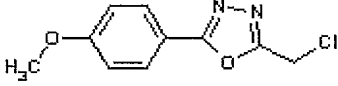
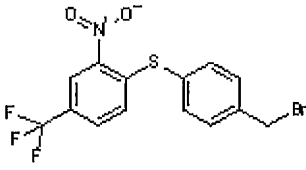
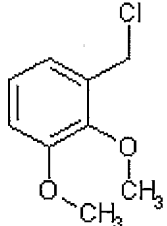
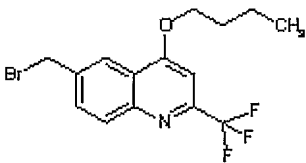
	224.646		177.064
	194.62		267.922
	262.617		350.235
	237.042		350.235
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	186.637		199.09
	169.035		199.09
	229.065		199.09

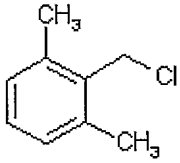
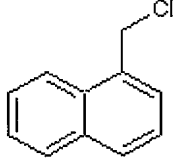
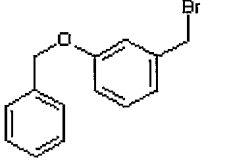
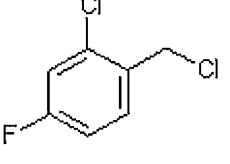
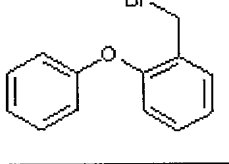
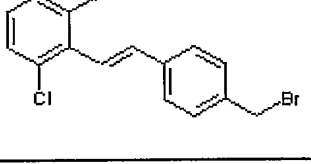
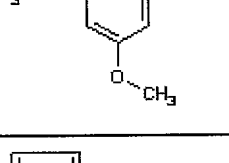
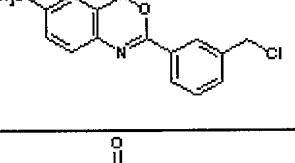
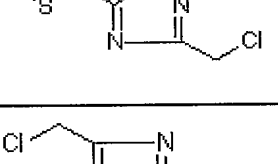
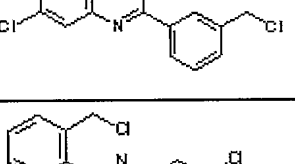
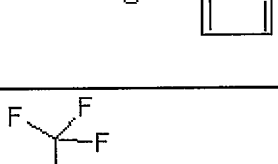
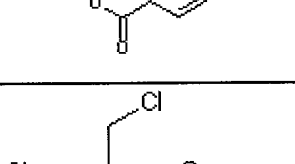
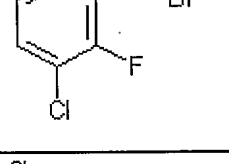
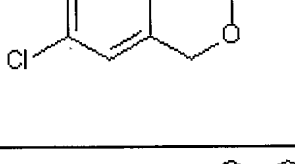
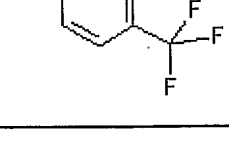
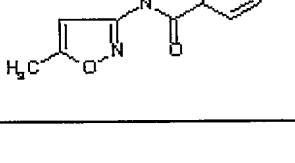
	250.727		199.09
	324.526		253.06
	261.569		258.103
	262.617		331.052
	273.699		88.5365
	249.127		132.988
	131.561		102.563
	210.581		144.644

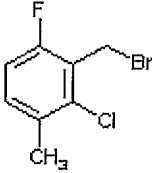
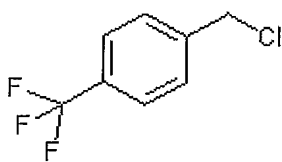
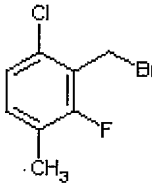
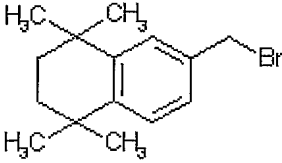
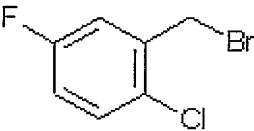
	303.154	ClH	144.044
		 (hydrochloride salt)	
	223.471	ClH	296.239
			
	179.02	ClH	172.098
			
	273.478	ClH	158.071
			
	257.023	ClH	170.082
			
	257.023	ClH	186.081
			

	241.12	ClH		184.109
	166.61		149.663	
	205.995	ClH		248.195
	188.613	ClH		313.064
	277.696	ClH		158.071
	133.602	ClH		186.124

	208.647		230.133
	272.144		129.589
	219.052		167.038
	229.065		
	209.699		
	226.648		
	132.613		

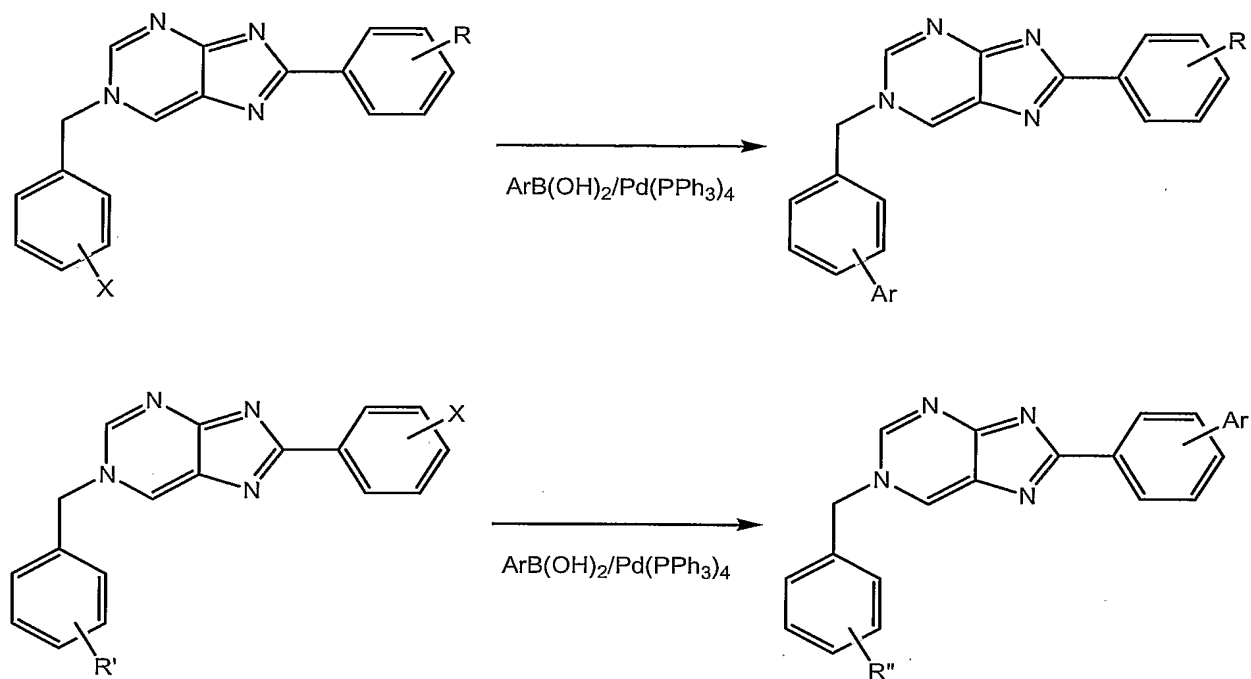
	207.659		
	223.471		
	276.549		
	168.047		
	162.566		
	224.646		
	186.637		

	154.639		
	277.16		
	263.133		
	231.088		
	200.648		
	215.727		
	291.469		
	273.478		

	237.498		
	237.498		
	223.471		

Scheme B shows a synthetic route to additional imidazopyrimidines.

Scheme B:

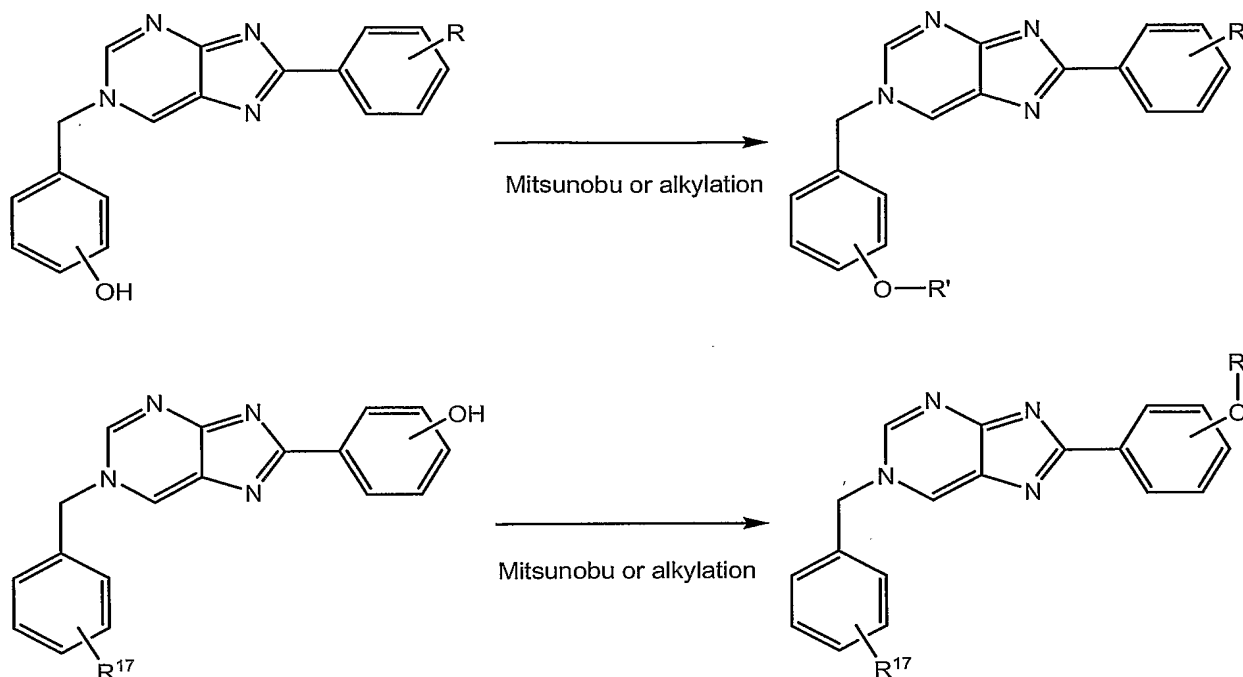


5 Scheme C shows a synthetic route to the compounds of this invention. R, R', and R'' can be any alkyl, benzylic or heterobenzylic groups.

10

15

20

Scheme C:

5

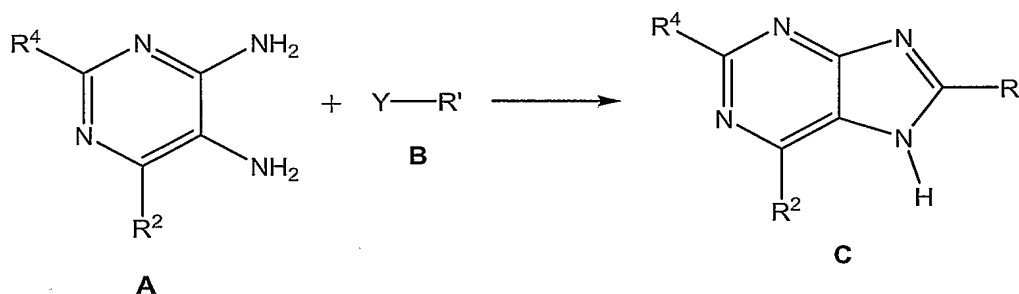
Analogous compounds may be synthesized in the same fashion as in the foregoing schemes by varying the starting materials, intermediates, solvents and conditions as will be known by those skilled in the art.

- An additional method for making the compounds of this invention involves reacting a (substituted) 3,4-diaminopyrimidine (A) with B (Y-R¹) to give imidazo[4,5-d]pyrimidines (C); introducing further substituents (R², R⁴ and/or R⁵ ≠ H) either a) by cyclization of an appropriately substituted 3,4-diaminopyrimidine (A) or b) by introduction of the substituent(s) onto the imidazo[4,5-d]pyrimidine (C); reacting the imidazo[4,5-c]pyrimidine (C) with an alkylating agent (D) (R³-X-R⁶) in an appropriate solvent under addition of a base at ambient temperature; and optionally, in the case of hydroxy, mercapto or amino substituents in position 4 or 6 of the imidazopyrimidine (Z = O, S or NR); introducing a further substituent (R²⁵ or R²⁶) at position 1 or 3 of the imidazo[4,5-d]pyrimidine.

Compounds of the invention also are conveniently prepared by a two step process. First, a (substituted) 3,4-diaminopyrimidine (A) is reacted with B to give imidazo[4,5-d]pyrimidines C (Scheme 1). If Y is COOH, then the cyclization is carried out under acidic catalysis (preferably in polyphosphoric acid at a temperature between 90 and 200°C); other methods include reaction in 4N hydrochloric acid at reflux temperature or neat at a temperature between 90 and 180°C (for aliphatic carboxylic acids). In the case of acid-sensitive groups like alkoxy or thiophene, the reaction can be carried out in phosphorus oxychloride at a temperature between 70 and 120°C. Alternatively, reaction with aldehydes (Y = CHO) or their bisulfite adducts under oxidative conditions (nitrobenzene, DDQ, copper(II)acetate, O₂, sulfur etc.) gives imidazo[4,5-d]pyrimidines C. Other methods are the reaction of (substituted) 3,4-diaminopyrimidines (A) with orthoesters (Y = C(OR)₃), anhydrides (Y = OCOOR) or acid halogenides (Y = COX), etc.

Further methods for the preparation of the compounds of the invention are set forth in Schemes 1-5 below.

Scheme 1:



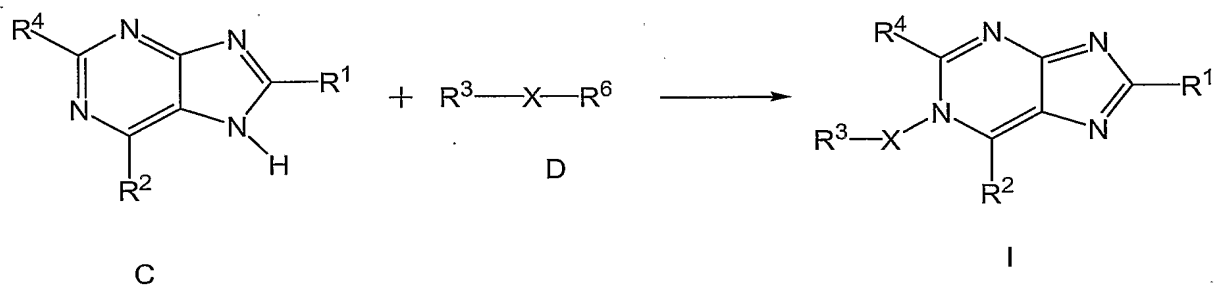
The imidazo[4,5-d]pyrimidines C are present in four tautomeric forms (1H, 3H, 4H, 6H).

Substituents, for example R² and R⁴, are introduced by two ways: i) by cyclization of an appropriately substituted 3,4-diaminopyrimidine or ii) by

introduction of the substituent(s) onto the imidazo[4,5-d]pyrimidine. Nitroamino pyrimidines are commercially available. Reduction of the nitro group with iron in a mixture of concentrated hydrochloric acid and ethanol gives the desired substituted 3,4-diaminopyrimidine starting materials.

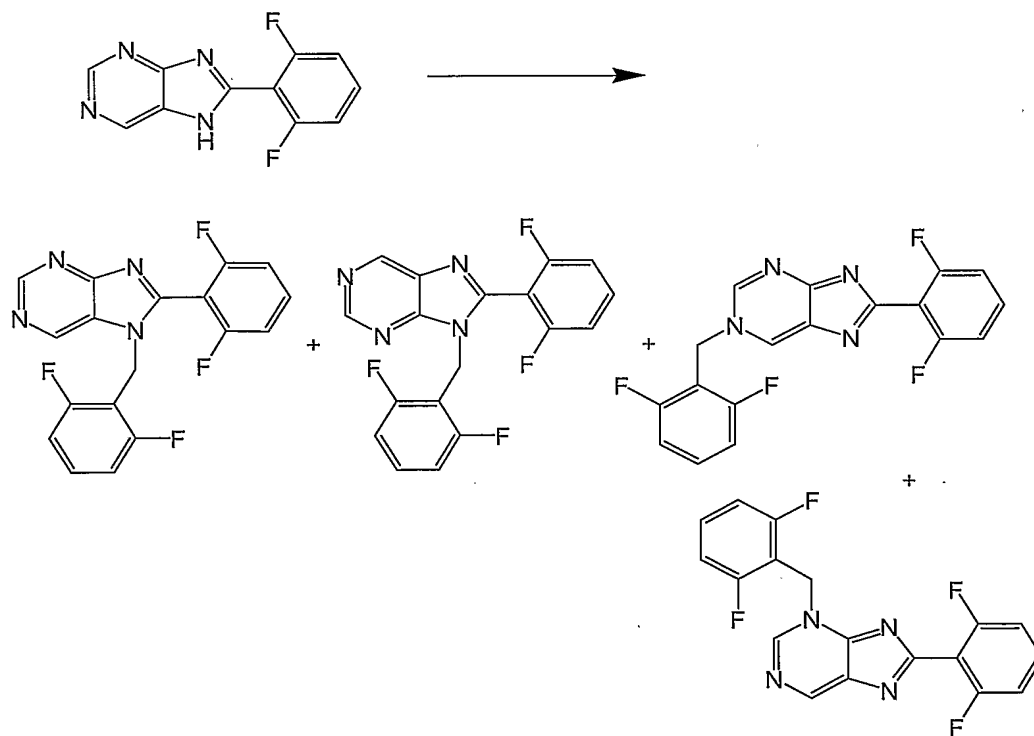
5

Scheme 2:



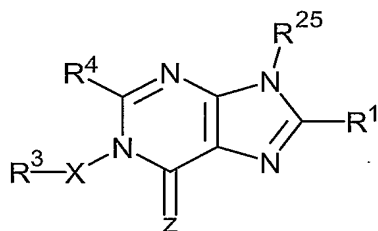
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This reaction gives mixtures of four alkylation products. For example, reaction of imidazo[4,5-d]pyrimidine C ($R^1 = 2,6$ -difluorophenyl, $R^2 = R^4 = H$) with 2,6-difluorobenzyl bromide would be expected to give the following mixture.

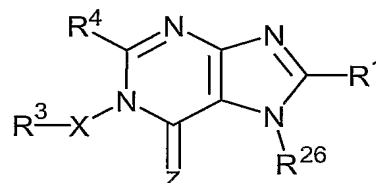


This mixture can be separated by column chromatography (silica gel, eluent: mixture of dichloromethane and methanol). The structures of the isolated components can then be assigned by NMR spectroscopy by single crystal x-ray analysis.

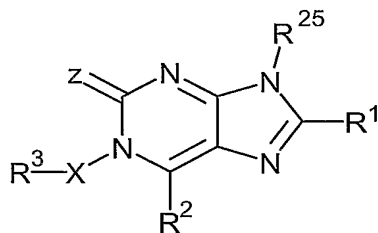
Alternatively, the crude reaction mixture can be recrystallized from an appropriate solvent (mixture), e.g. from a mixture of diisopropyl ether and ethyl acetate, to give the pure alkylated products.



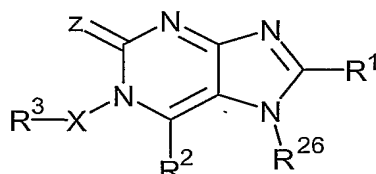
E



F



G

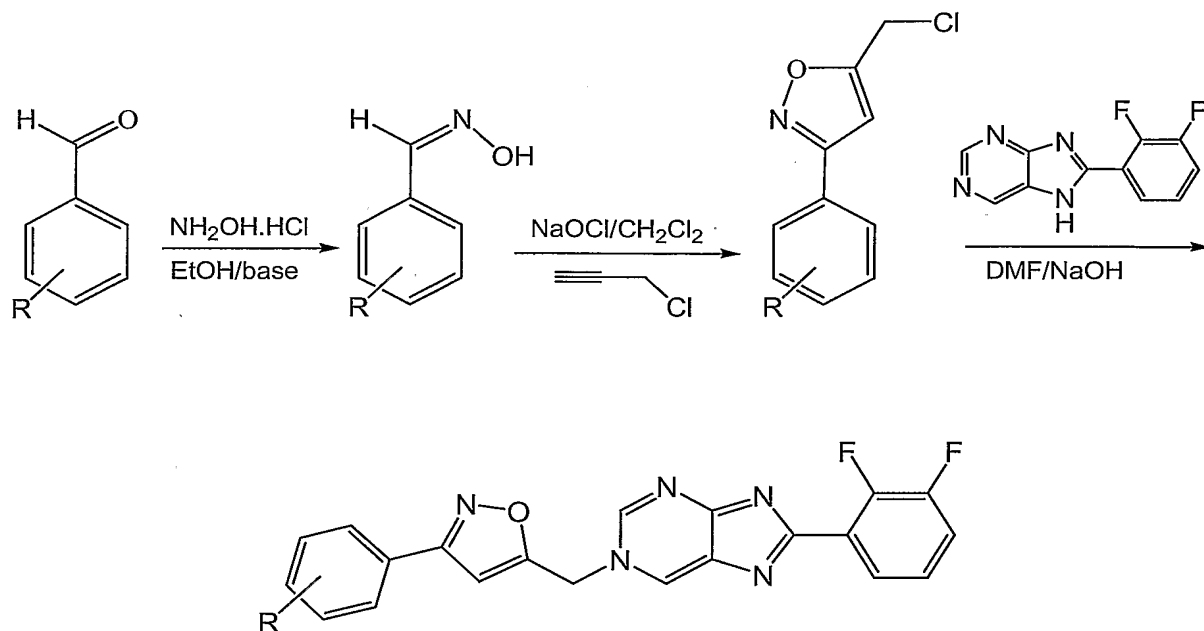


H

Compounds of general structure E, F, G and H can be prepared by alkylation (for example with (cyclo)alkylbromide or (cyclo)alkyliodide etc.) of the corresponding compounds where Z=O, Z=S or Z=NR or their isomers. The resulting mixtures can be separated by column chromatography. The required starting materials are, for example, prepared from the corresponding chloro-analogues by nucleophilic substitution, or by ether cleavage of the corresponding alkoxy analogues.

Scheme 3

Isoxazole Telescoping Scheme



R=R¹⁹; further embodiments comprise replacing phe-R with other R¹⁷.

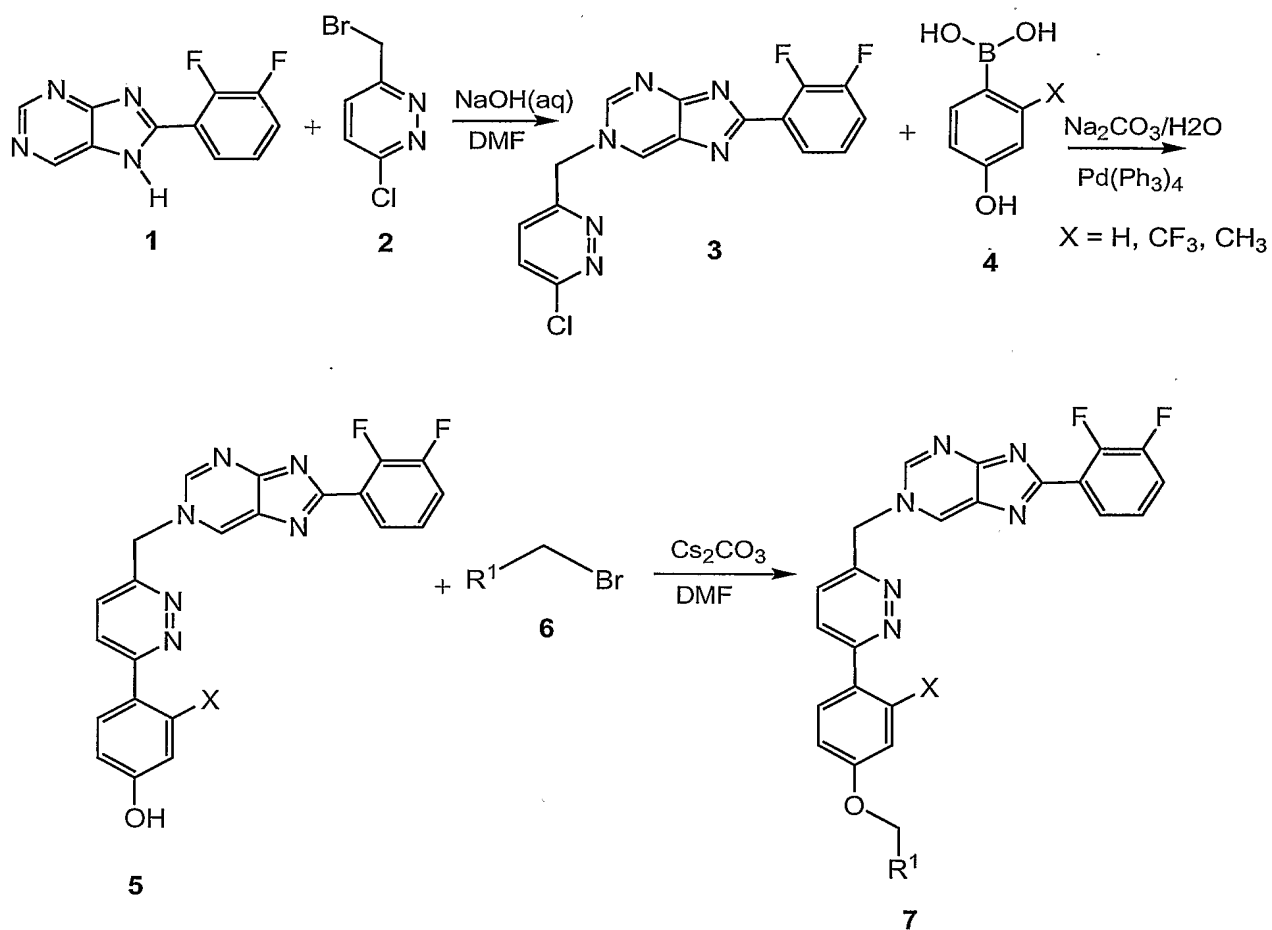
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5 Scheme 4

Preparation of Pyridazine Phenyl Alkoxy Array



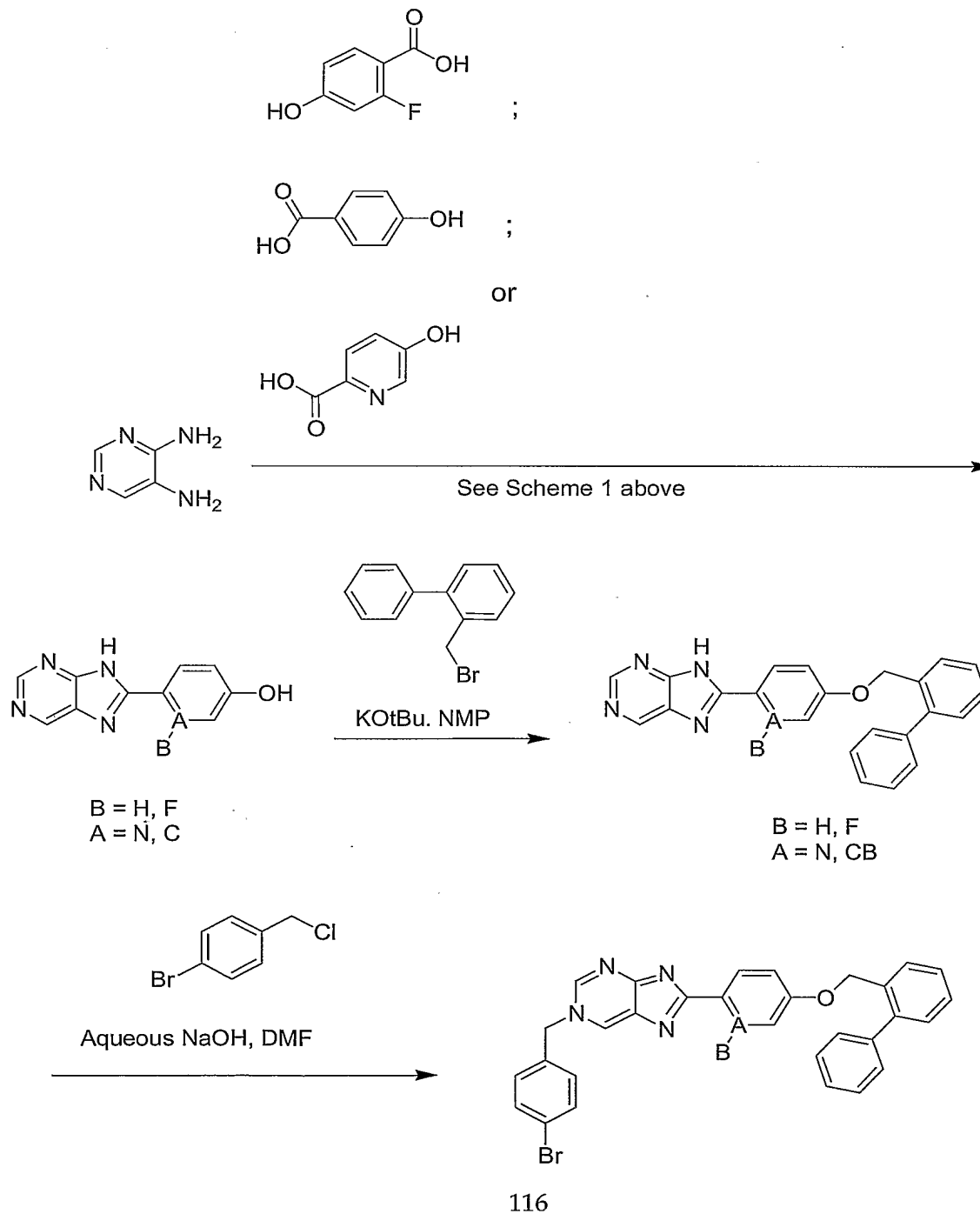
10

Further embodiments: Replace 2 with other bromides consistent with R³, replace 4 with other R¹⁷ precursors.

15

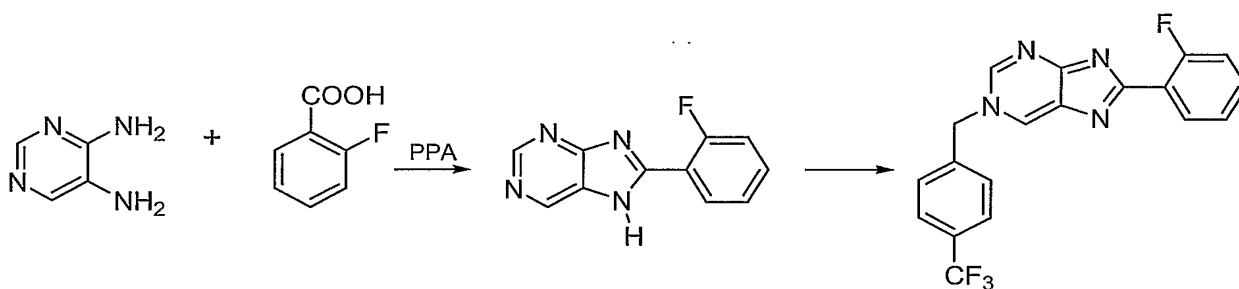
Scheme 5 shows further examples for the synthesis of compounds with a substituted (het)aryl of the imidazo[4,5-d]pyrimidine ring system.

5 Scheme 5:



Analogous compounds are synthesized in the same fashion as in the foregoing schemes and the following examples by varying the starting materials, intermediates, solvents and conditions as will be known by those skilled in the art.

Example 1



A.

8-(2-Fluorophenyl)-purine

A mixture of 4,5-diaminopyrimidine (0.500 g), 2-fluorobenzoic acid (0.700 g) and polyphosphoric acid (25 mL) was heated at 180°C for 3 hours. Then the reaction mixture was cooled and poured into water (500 mL). The solution was adjusted to pH = 8-9 by addition of solid NaOH and the resulting precipitate was collected by filtration, washed with water and dried to give 8-(2-fluorophenyl)-purine (off-white powder, 88.5%).

¹H NMR (200 MHz, DMSO-d₆) δ 13.79 (br s, 1H, NH), 9.14 (s, 1H, purine-H), 8.95 (s, 1H, purine-H), 8.23 (m, 1H, phenyl-H), 7.73-7.41 (m, 3H, phenyl-H).

B.

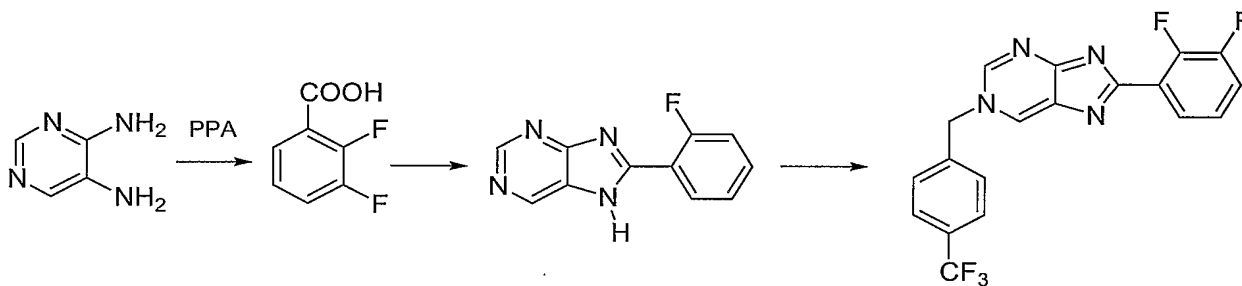
8-(2-Fluorophenyl)-1-[(4-trifluoromethyl)phenylmethyl]-1H-purine

8-(2-Fluorophenyl)-purine (430 mg) was dissolved in dry DMF (4 mL), aqueous 30% NaOH solution (400 mg) was added and the resulting mixture was stirred for 30 minutes. Then, 4-(trifluoromethyl)benzyl chloride (469 mg) was added and the

resulting mixture was stirred for 1 day at ambient temperature. Water (200 mL) was added and the resulting solution was extracted with ethyl acetate (3 x 70 mL). The combined ethyl acetate phases were dried (Na_2SO_4) and evaporated. The residue was recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (30 mL) to give 8-(2-fluorophenyl)-1-[(4-trifluoromethyl)phenylmethyl]-1H-purine (GPJN-179) as an off-white powder (yield: 18.9 %, m.p.: 251-256°C).

^1H NMR (200 MHz, $\text{DMSO}-d_6$) δ 9.25 (d, 1H, purine-H, $J=2.0$ Hz), 9.14 (d, 1H, purine-H, $J=2.0$ Hz), 8.33 (m, 1H, phenyl-H), 7.83-7.65 (AA'BB', 4H, benzyl-H), 7.53 (m, 1H, phenyl-H); 7.38-7.27 (m, 2H, phenyl-H), 5.78 (s, 2H, CH_2).

Example 2



A.

8-(2,3-Difluorophenyl)-purine

Synthesized as described above for 8-(2-fluorophenyl)-purine, except that 2,3-difluorobenzoic acid was used instead of 2-fluorobenzoic acid (white powder, yield: 45.7%)

^1H NMR (200 MHz, $\text{DMSO}-d_6$) δ 13.70 (br s, 1H, NH), 9.18 (s, 1H, purine-H), 8.97 (s, 1H, purine-H), 8.04-7.96 (m, 1H, phenyl-H), 7.78-7.64 (m, 1H, phenyl-H), 7.52-7.40 (m, 1H, phenyl-H).

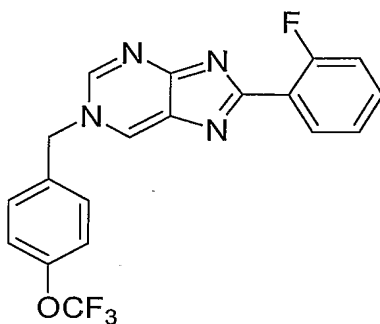
B.

8-(2,3-Difluorophenyl)-1-[(4-trifluoromethyl)phenylmethyl]-1H-purine

Synthesized as described above for Example 1, except that 8-(2,3-difluorophenyl)-purine was used instead of 8-(2-fluorophenyl)-purine (white powder, yield: 9.4%, m.p.: 267-271°C).

¹H NMR (200 MHz, DMSO-d₆) δ 9.33 (d, 1H, purine-H, J=2.0 Hz), 9.17 (d, 1H, purine-H, J=2.0 Hz), 8.14 (m, 1H, phenyl-H), 7.82-7.67 (AA'BB', 4H, benzyl-H), 7.62-7.49 (m, 1H, phenyl-H), 7.40-7.28 (m, 1H, phenyl-H), 5.79 (s, 2H, CH₂).

5 Example 3

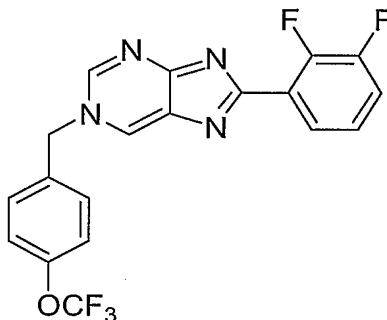


Synthesized as described above for Example 1, except that 4-
10 (trifluoromethoxy)benzyl bromide was used instead of 4-(trifluoromethyl)benzyl chloride (white powder, yield: 11.2%, m.p.: 224-228°C).

¹H NMR (200 MHz, DMSO-d₆) δ 9.24 (d, 1H, purine-H, J=2.0 Hz), 9.13 (d, 1H, purine-H, J=2.0 Hz), 8.31 (m, 1H, phenyl-H), 7.66-7.26 (m, 6H, 4 benzyl-H, 2 phenyl-H), 5.69 (s, 2H, CH₂).

15

Example 4

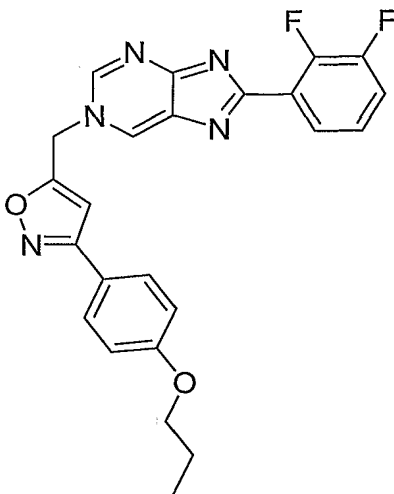


20 Synthesized as described above for Example 2, except that 4-(trifluoromethoxy)benzyl bromide was used instead of 4-(trifluoromethyl)benzyl chloride (gray powder, yield: 21.5%, m.p.: 254-258°C).

^1H NMR (200 MHz, DMSO- d_6) δ 9.34 (d, 1H, purine-H, $J=2.0$ Hz), 9.19 (d, 1H, purine-H, $J=2.0$ Hz), 8.14 (m, 1H, phenyl-H), 7.68-7.41 (AA'BB', 4H, benzyl-H), 7.59-7.29 (m, 2H, phenyl-H), 5.72 (s, 2H, CH_2).

5

Example 5



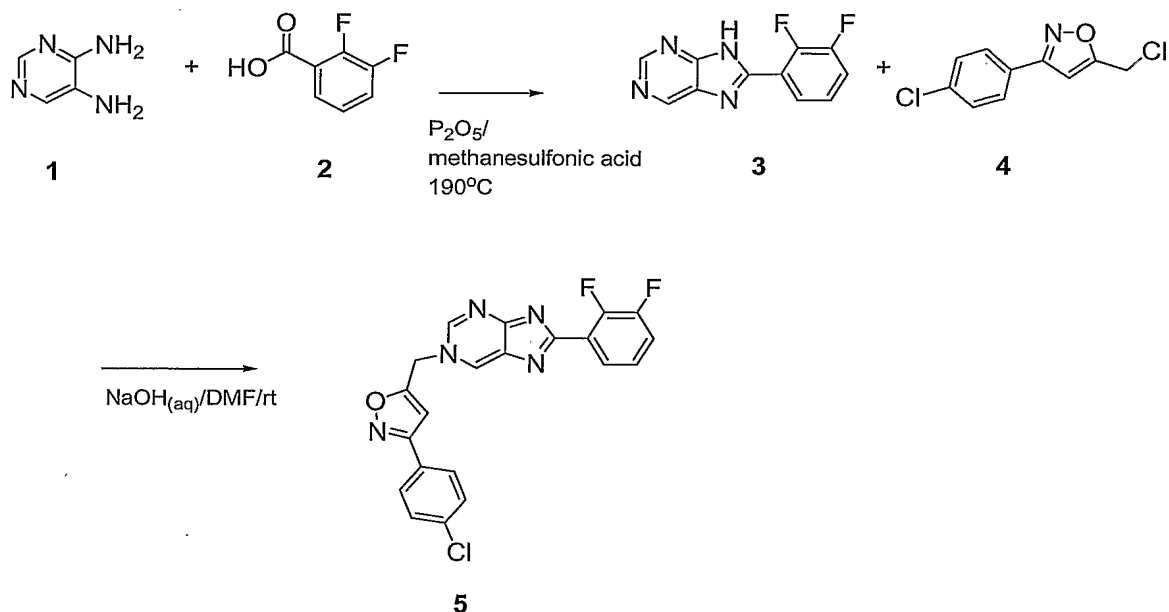
- 10 Synthesized as described above for Example 2, except that 5-chloromethyl-3-(4-propoxyphenyl)-isoxazole was used instead of 4-(trifluoromethyl)benzyl chloride. Purified by column chromatography (silica gel, eluent: dichloromethane : methanol = 20 : 1), followed by recrystallization (diisopropyl ether/ethyl acetate). Colourless crystals, yield: 7.4%, m.p.: 228-231°C).
- 15 ^1H NMR (200 MHz, DMSO- d_6) δ 9.34 (d, 1H, purine-H, $J=2.0$ Hz), 9.15 (d, 1H, purine-H, $J=2.0$ Hz), 8.17 (m, 1H, phenyl-H), 7.88-7.08 (AA'BB', 4H, benzyl-H), 7.63-7.48 (m, 1H, phenyl-H), 7.41-7.30 (m, 1H, phenyl-H), 7.01 (s, 1H, isoxazole-H), 5.98 (s, 2H, CH_2), 3.98 (t, 2H, OCH_2 , $J=6.6$ Hz), 1.73 (hex, 2H, CH_2 , $J=6.6$ Hz), 0.97 (t, 3H, CH_3 , $J=6.6$ Hz).

20

Example 6

Preparation of 1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-8-(2,3-difluorophenyl)-1H-purine

5



4,5-Diaminopyrimidine (**1**) (4.5 g, 0.04 moles) and 2,3-difluorobenzoic acid (**2**) (6.95 g, 0.044 moles) were suspended in 100 mL of Eaton's Acid. The reaction mixture was heated in an oil bath at 190°C for 2 hours and then poured into 800mL ice/water. Solid sodium hydroxide was added (59g, 1.5 moles) to adjust to pH 5, which resulted in the product precipitating from solution. The product was filtered and washed twice with deionized water and air dried. The crude product was recrystallized from water/ethanol resulting in 8 g of pure product (**3**) ($M+1 = 233$).

Purine (**3**) (500 mg, 2.15 mmoles) was dissolved in 10mL of anhydrous DMF and 1.1 mL of sodium hydroxide solution (10% w/v) was added. 5-(Chloromethyl)-3-(4-chlorophenyl)isoxazole (**4**) (587 mg, 2.6 mmoles) was added to the above reaction mixture and the solution was stirred at room temperature overnight. The crude product was triturated from water followed by recrystallization from hot ethyl acetate. The precipitate was filtered to yield 30mg of the gold colored solid

1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-8-(2,3-difluorophenyl)-1H-purine (5) in high purity as determined by analytical LC/MS ($M+1 = 429$) and ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 5.99 (s, 2H), 7.17 (s, 1H), 7.34 (m, 1H), 7.55 (s, 1H), 7.56 (d, 2H), 7.87 (d, 2H), 8.14 (m, 1H), 9.14 (s, 1H), 9.32 (s, 1H).

5 Example 7

Determination of antiviral (EC_{50}) and cytostatic activity (CC_{50})

Cells and viruses

10 Madin-Darby Bovine Kidney (MDBK) cells were maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with BVDV-free 5% fetal calf serum (DMEM-FCS) at 37°C in a humidified, 5% CO_2 atmosphere.

Determination of cytostatic effect on MDBK cells

15 The effect of the drugs on exponentially growing MDBK cells was assessed as follows. Cells were seeded at a density of 5000 cell/well in 96 well plates in MEM medium (Gibco) supplemented with 10% fetal calf serum, 2mM L-glutamine (Life Technologies) and bicarbonate (Life Technologies). Cells were cultured for 24 hr after which serial dilutions of the test compounds were added.
20 Cultures were then again further incubated for 3 days after which the effect on cell growth was quantified by means of the MTS method (Promega). The concentration that results in 50% inhibition of cell growth is defined as the 50 % cytostatic concentration (CC_{50}).

25 Anti-HCV assay / Replicon assay

Huh-5-2 cells [a cell line with a persistent HCV replicon I389luc-ubi-neo/NS3-3'/5.1; replicon with firefly luciferase-ubiquitin-neomycin phosphotransferase fusion protein and EMCV-IRES driven NS3-5B HCV polyprotein] was cultured in RPMI medium (Gibco) supplemented with 10% fetal
30 calf serum, 2mM L-glutamine (Life Technologies), 1x non-essential amino acids (Life Technologies); 100 IU/ml penicillin and 100 ug/ml streptomycin and 250

ug/ml G418 (Geneticin, Life Technologies). Cells were seeded at a density of 7000 cells per well in 96 well View Plate™ (Packard) in medium containing the same components as described above, except for G418. Cells were allowed to adhere and proliferate for 24 hr. At that time, culture medium was removed and serial dilutions of the test compounds were added in culture medium lacking G418. Interferon alfa 2a (500 IU) was included as a positive control. Plates were further incubated at 37°C and 5% CO₂ for 72 hours. Replication of the HCV replicon in Huh-5 cells results in luciferase activity in the cells. Luciferase activity is measured by adding 50 µl of 1 × Glo-lysis buffer (Promega) for 15 minutes followed by 50 ul of the Steady-Glo Luciferase assay reagent (Promega). Luciferase activity is measured with a luminometer and the signal in each individual well is expressed as a percentage of the untreated cultures. Parallel cultures of Huh-5-2 cells, seeded at a density of 7000 cells/ well of classical 96-well cell culture plates (Becton-Dickinson) are treated in a similar fashion except that no Glo-lysis buffer or Steady-Glo Luciferase reagent is added. Instead the density of the culture is measured by means of the MTS method (Promega).

Quantitative analysis of HCV RNA by Taqman real-time RT-PCR

Replicon cells were plated at 7.5×10^3 cells per well in a 96-well plate plates at 37°C and 5% CO₂ in Dulbecco's modified essential medium containing 10% fetal calf serum, 1% nonessential amino acids and 1 mg/ml Geneticin. After allowing 24 h for cell attachment, different dilutions of compound were added to the cultures. Plates were incubated for 5 days, at which time RNA was extracted using the Qiaamp Rneasyi Kit (Qiagen, Hilden, Germany). A 50 µL PCR reaction contained TaqMan EZ buffer (50 mmol/L Bicine, 115 mmol/L potassium acetate, 0.01 mmol/L EDTA, 60 nmol/L 6-carboxy-X-rhodamine, and 8% glycerol, pH 8.2; Perkin Elmer Corp./Applied Biosystems), 300 µmol/L deoxyadenosine triphosphate, 300 µmol/L deoxyguanosine triphosphate, 300 µmol/L deoxycytidine triphosphate, 600 µmol/L deoxyuridine triphosphate, 200 µmol/L forward primer [5'-ccg gcT Acc Tgc ccA TTc], 200 µmol/L reverse primer [ccA GaT cAT ccT gAT cgA cAA G], 100 µmol/L TaqMan probe [6-FAM-AcA Tcg cAT

cgA gcg Agc Acg TAc-TAMRA], 3 mmol/L manganese acetate, 0.5 U AmpErase uracil-*N*-glycosylase, 7.5 U rTth DNA polymerase, and 10 µl of RNA elution.

After initial activation of uracil-*N*-glycosylase at 50°C for 2 minutes, RT was performed at 60°C for 30 minutes, followed by inactivation of uracil-*N*-

5 glycosylase at 95°C for 5 minutes. Subsequent PCR amplification consisted of 40 cycles of denaturation at 94°C for 20 seconds and annealing and extension at 62°C for 1 minute in an ABI 7700 sequence detector. For each PCR run, negative template and positive template samples were used. The cycle threshold value (Ct-value) is defined as the number of PCR cycles for which the signal exceeds the
10 baseline, which defines a positive value. The sample was considered to be positive if the Ct-value was <50. Results are expressed as genomic equivalents (GE).

Example 8

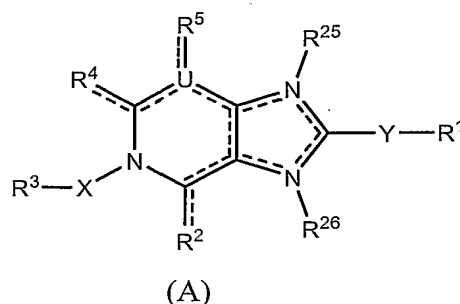
Assay Results

15 All of the compounds of examples 1-6 exhibited excellent anti-HCV antiviral activity and low toxicity.

20

We Claim:

1. A compound of formula (A)



- 5 wherein:

the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

U is N;

- 10 R¹ is selected from hydrogen, aryl, heterocycle, C₁-C₁₀ alkoxy, C₁-C₁₀ thioalkyl, C₁-C₁₀ alkyl-amino, C₁-C₁₀ dialkyl-amino, C₃₋₁₀ cycloalkyl, C₄₋₁₀ cycloalkenyl, and C₄₋₁₀ cycloalkynyl, wherein each are optionally substituted with 1 or more R⁶;

- 15 Y is selected from a single bond, O, S(O)_m (where m is an integer from 0 to 2), NR¹¹, C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, and C₂₋₁₀ alkynylene, or C₁₋₁₀ alkylene, C₂₋₂₀ alkenylene or C₂₋₁₀ alkynylene, wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR¹¹;

- 20 R² and R⁴ are independently selected from hydrogen, C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, C₂₋₁₈ alkynyl, C₁₋₁₈ alkoxy, C₁₋₁₈ alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸, haloalkyloxy, haloalkyl, -C(=O)R⁹, -C(=S)R⁹, SH, aryl, aryloxy, arylthio, arylalkyl, C₁₋₁₈ hydroxyalkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyloxy, C₃₋₁₀ cycloalkylthio, C₃₋₁₀ cycloalkenyl, C₇₋₁₀ cycloalkynyl, and heterocycle, provided that when one of R²⁵ or R²⁶ is present, then either R² or R⁴ is selected from =O, =S, or =NR²⁷;

X is selected from C_1 - C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, where each may include one or more heteroatoms selected from O, S, or NR^{11} , provided any such heteroatom is not adjacent to the N in the ring;

5 R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl- $N(R^{10})$ -, or heterocycle, where each said substituent is optionally substituted with at least one R^{17} , provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, - NO_2 , - NR^7R^8 , haloalkyloxy, haloalkyl, - $C(=O)R^9$, - $C(=O)OR^9$, - $C(=S)R^9$, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, and heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl, - CO_2R^{18} , NO_2 , - NR^7R^8 , C_{1-18} haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, and C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19} ;

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, - $C(=O)R^{12}$; - $C(=S)R^{12}$, an amino acid residue linked through a carboxyl group thereof, and the group formed when R^7 and R^8 are taken together with the nitrogen to form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, - $NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1 - C_{12} alkyl, C_6 - C_{20} aryl, C_6 - C_{20} alkylaryl or C_6 - C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, and an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, arylalkyl (unsubstituted, or substituted with $C(O)OR^{18}$), C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{17} is independently selected from the group consisting of (a) hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halogenated alkyl, C_{2-18} halogenated alkenyl, C_{2-18} halogenated alkynyl, C_{1-18} halogenated alkoxy, C_{1-18} halogenated alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, CO_2H , CO_2R^{18} , NO_2 , NR^7R^8 , haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH; aryl, heterocycle, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle and C_{1-18} hydroxyalkyl, where each of said aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle, or C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} , and (b) M-Q- wherein M is a ring optionally substituted with 1 or more R^{19} , and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R^{19} ;

R^{19} is selected from

(a) H;

(b) NO_2 , SH, $NR^{20}R^{21}$, OH, halogen and CN;

(c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20} , $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or

$N(R^{20})C(O)$;

- (f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;
- (g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}=O$, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;
- (h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;
- (i) Substituents d) or e) substituted with $=O$, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle, and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, $=O$, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;
- (j) Substituents c) substituted further with C_{1-18} alkyl; and
- (k) Substituents f) or g) substituted further with C_{1-18} alkyl, $=O$, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, and $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , benzyloxy, and OH;

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, $(C_{3-10}$ cycloalkyl)- C_{1-6} alkyl, aryl, and aryl- C_{1-18} alkyl; and salts, tautomers, polymorphs, isomers and solvates thereof.

2. The compound of claim 1 wherein R^1 is haloaryl, X is methylene, R^3 is heterocycle substituted with 1 or 2 R^{17} .

3. The compound of claim 1 wherein R^1 is an aryl or aromatic heterocycle substituted with 1 or 2 R^6 .

4. The compound of claim 1 wherein R^3 is heterocycle.
5. The compound of claim 1 wherein YR^1 is haloaryl.
- 5 6. The compound of claim 5 wherein haloaryl is ortho-fluorophenyl.
7. The compound of claim 1 wherein R^3 is isoxazolyl substituted with 1 R^{17} .
- 10 8. The compound of claim 2 wherein R^{17} is aryl or an aromatic heterocycle which is substituted with 1, 2 or 3 R^{19} .
9. The compound of claim 1 wherein YR^1 is none of hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl.
- 15 10. The compound of claim 9 wherein YR^1 is not hydrogen or C_{1-6} alkyl.
11. The compound of claim 1 wherein R^{19} is trihalomethyl, trihalomethoxy, alkoxy or halogen.
- 20 12. The compound of claim 1 wherein R^1 is aryl or aromatic heterocycle substituted with 1, 2 or 3 R^6 wherein R^6 is halogen, C_{1-18} alkoxy; or C_{1-18} haloalkyl.
13. The compound of claim 12 wherein R^1 is phenyl substituted with 1, 2 or 3
25 halogens.
14. The compound of claim 13 wherein halogen is fluoro.

15. The compound of claim 1 wherein Y is a single bond, O, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene or one of said groups containing 1 to 3 heteroatoms selected from O, S or NR¹¹.
- 5 16. The compound of claim 15 wherein Y is -O(CH₂)₁₋₅-, -(CH₂)₁₋₄-O-(CH₂)₁₋₄-, -S-(CH₂)₁₋₅-, -(CH₂)₁₋₄-S-(CH₂)₁₋₄-, -NR¹¹-(CH₂)₁₋₅-, -(CH₂)₁₋₄-NR¹¹-(CH₂)₁₋₄ or C₃₋₁₀ cycloalkylidene.
17. The compound of claim 15 wherein Y is -OCH₂-, -CH₂O-, C₁₋₂ alkylene, C₂₋₃ alkenylene, C₂₋₃ alkynylene, O or a bond.
- 10 18. The compound of claim 15 wherein Y is a bond.
19. The compound of claim 1 wherein YR¹ is a single ring aromatic carbocycle or a heterocycle containing 1 or 2 N, S or O atoms in the ring.
- 15 20. The compound of claim 19 wherein the carbocycle or heterocycle contains 4 to 6 ring atoms.
- 20 21. The compound of claim 1 wherein YR¹ is halo- or halomethyl-substituted phenyl.
22. The compound of claim 1 wherein aryl or heteroaryl are substituted ortho or meta with halo- or halomethyl.
- 25 23. The compound of claim 1 wherein X is selected from the group consisting of alkylene, alkynylene or alkenylene and said hydrocarbons having an intrachain N, O or S heteroatom.
- 30 24. The compound of claim 1 wherein X is alkylene.

25. The compound of claim 23 wherein X is selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-(\text{CH}_2)_{2-4}-\text{O}-$, $(\text{CH}_2)_{2-4}-$, $-(\text{CH}_2)_{2-4}-\text{S}-(\text{CH}_2)_{2-4}-$, $-(\text{CH}_2)_{2-4}-\text{NR}^{10}-(\text{CH}_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene and C_{2-6} alkynylene.

5

26. The compound of claim 1 wherein X is methylene.

27. The compound of claim 1 wherein R^3 is aryl or a heterocycle substituted with 0 to 3 R^{17} .

10

28. The compound of claim 27 wherein the heterocycle is an aromatic heterocycle.

29. The compound of claim 28 wherein the heterocycle contains 1, 2 or 3 N, S or O atoms in the ring, is linked to X through a ring carbon atom and contains 4 to 6 total ring atoms.

15

30. The compound of claim 29 wherein R^3 is isoxazolyl substituted with 1 to 3 R^{17} .

20

31. The compound of claim 1 wherein R^{17} is aryl or a heterocycle further substituted with 1 to 3 R^{19} .

32. The compound of claim 1 wherein M is aryl or aromatic heterocycle.

25

33. The compound of claim 1 wherein Q contains 0 to 20 atoms selected from C, O, S, N and H.

34. The compound of claim 1 wherein M is a cyclic group selected from R^{17} .

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35. The compound of claim 1 wherein R^{17} is selected from the group consisting of C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy; arylalkylthio; heterocycle; C_{1-18} hydroxyalkyl, each of said C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy; arylalkylthio; heterocycle; and C_{1-18} hydroxyalkyl is unsubstituted or is substituted 1 or more R^{19} .
36. The compound of claim 1 wherein R^{17} is selected from the group consisting of aryl and heterocycle, and where said aryl or heterocycle is optionally substituted with 1 or more R^{19} .
37. The compound of claim 1 wherein R^9 and R^{18} are H, OH or alkyl.
38. The compound of claim 1 wherein R^5 is H.
39. The compound of claim 1 wherein R^6 is halogen.
40. The compound of claim 1 wherein R^7 , R^8 , R^{10} , R^{11} , R^{15} , R^{16} , R^{20} , and R^{21} are independently H or C_{1-18} alkyl.
41. The compound of claim 1 wherein R^{12} is OH or alkyl.
42. The compound of claim 1 wherein R^{19} is selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; alkenyloxy; alkynyloxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{4-10} cycloalkenyl; C_{4-10} cycloalkynyl; halogen; OH; CN; cyanoalkyl; NO_2 ; $NR^{20}R^{21}$; haloalkyl; haloalkyloxy; $C(=O)R^{18}$; $C(=O)OR^{18}$; $OalkenylC(=O)OR^{18}$; $-OalkylC(=O)NR^{20}R^{21}$; aryl; heterocycle; $-OalkylOC(=O)R^{18}$; $C(=O)N(C_{1-6} alkyl)$, $N(H)S(O)(O)(C_{1-6} alkyl)$; arylalkyloxy; aryloxy; arylalkyloxy; and arylalkyl.

43. The compound of claim 42 wherein R^{19} is independently selected from the group consisting of halogen, $N(R^{20} R^{21})$, alkoxy, halo-substituted alkyl and halo-substituted alkoxy.

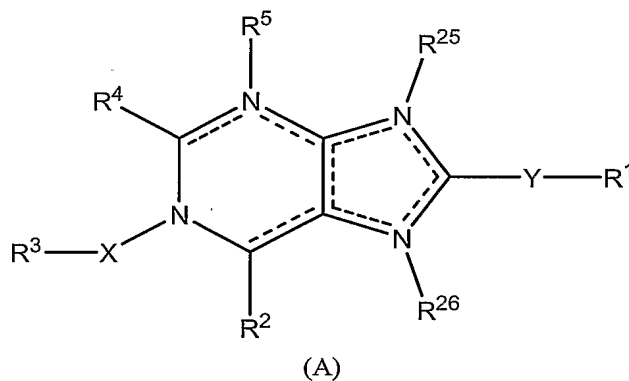
5 44. The compound of claim 1 wherein R^{25} and R^{26} are not present.

45. The compound of claim 1 which is not substituted at R^{25} but is substituted at R^{26} , and either R^2 or R^4 is selected from $(=O)$, $(=S)$, and $(=NR^{27})$.

10 46. The compound of claim 1 wherein haloalkyl or haloalkyloxy is $-CF_3$ or $-OCF_3$.

47. The compound of claim 1 wherein R^{19} is any individual, combination or subcombination of substituents (a) – (k).

15 48. A compound having the general formula (A),



wherein:

20 the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

R^1 is selected from hydrogen, aryl, heterocycle (other than piperazinyl, piperidinyl, or either substituted with 1 or more R^6), C_1 - C_{10} alkoxy, C_1 - C_{10} thioalkyl,

C_{1-10} alkyl-amino, C_{1-10} dialkyl-amino, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or more R^6 ;

Y is selected from a single bond, O, S(O)_m (where m is an integer from 0 to 2), NR^{11} , C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, or C_{1-10} alkylene, C_{2-20} alkenylene or C_{2-10} alkynylene wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR^{11} ; provided, however, that YR^1 is not H;

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO₂, - NR^7R^8 , haloalkyloxy, haloalkyl, -C(=O) R^9 , -C(=S) R^9 , SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from (=O), (=S), and = NR^{27} ; and further provided that not both of R^2 and R^4 is OH, SH, thio or oxo;

X is selected from C_{1-10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, where each may include one or more heteroatoms selected from O, S, or NR^{11} , provided any such heteroatom is not adjacent to the N in the ring;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R^{10})-, or heterocycle, where each said substituent may be optionally substituted with at least one R^{17} , provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO₂, - NR^7R^8 , haloalkyloxy, haloalkyl, -C(=O) R^9 , -C(=O)OR⁹, -C(=S) R^9 , SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl,

$-\text{CO}_2\text{R}^{18}$, NO_2 , $-\text{NR}^7\text{R}^8$, C_{1-18} haloalkyl, $\text{C}(=\text{O})\text{R}^{18}$, $\text{C}(=\text{S})\text{R}^{18}$, SH , aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19} ;

5 R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, $-\text{C}(=\text{O})\text{R}^{12}$, $-\text{C}(=\text{S})\text{R}^{12}$, an amino acid residue linked through a carboxyl group thereof, or where R^7 and R^8 together with the nitrogen form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH , C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, $-\text{NR}^{15}\text{R}^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $\text{CH}_2\text{OCH}(=\text{O})\text{R}^{9a}$, or $\text{CH}_2\text{OC}(=\text{O})\text{OR}^{9a}$ where R^{9a} is $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_6\text{-C}_{20}$ aryl, $\text{C}_6\text{-C}_{20}$ alkylaryl or $\text{C}_6\text{-C}_{20}$ aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of
15 hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-\text{C}(=\text{O})\text{R}^{12}$, heterocycle, or an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{17} is independently M-Q- wherein M is a ring optionally substituted with 1 or more R^{19} , and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally
25 substituted with 1 or more R^{19} ;

R^{19} is selected from

(a) H;

(b) NO_2 , SH , $\text{NR}^{20}\text{R}^{21}$, OH , halogen and CN;

30 (c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20} , $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}=O$, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with $=O$, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, $=O$, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

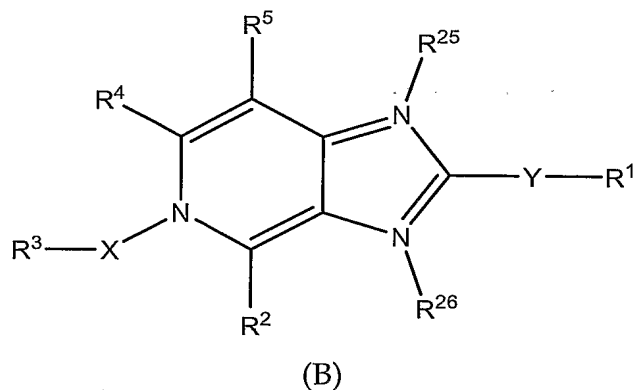
(k) Substituents f) or g) substituted further with C_{1-18} alkyl, $=O$, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, or $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , benzyloxy, and OH; and

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, $(C_{3-10}$ cycloalkyl)- C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl, and salts, tautomers, polymorphs, isomers and solvates thereof.

49. The compound of claim 48 wherein Y is a single bond, and R¹ is aryl or aromatic heterocycle which is unsubstituted or substituted with one or more R⁶.
50. The compound of claim 48 wherein X is C₁-C₁₀ alkylene, C₂₋₁₀ alkenylene or
 5 C₂₋₁₀ alkynylene.
51. The compound of claim 48 wherein R³ is heterocycle.
52. The compound of claim 48 wherein R³ is heterocycle substituted with R¹⁷
 10 where Q is a bond and M is aryl substituted with 1 or 2 R¹⁹.
53. The compound of claim 48 wherein Y is a single bond, and R¹ is phenyl.
54. The compound of claim 48 wherein R³ is isoxazole substituted with R¹⁷
 15 where Q is a bond and M is aryl substituted with 1 or 2 R¹⁹.
55. The compound of claim 48 wherein R³ is isoxazole substituted with R¹⁷
 where Q is a bond and M is phenyl substituted with 1 or 2 R¹⁹.
- 20 56. A compound having the general formula (B),



wherein:

R^1 is selected from aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or 2 R^6 ;

Y is a bond;

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸, haloalkyloxy, haloalkyl, -C(=O)R⁹, -C(=S)R⁹, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from (=O), (=S), and =NR²⁷; provided that R^2 is not OH, SH, thio or oxo;

X is selected from C_1 - C_3 alkylene, C_{2-3} alkenylene or C_{2-3} alkynylene;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R^{10})-, or heterocycle, where each is optionally substituted with at least one R^{17} , provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO₂, -NR⁷R⁸, haloalkyloxy, haloalkyl, -C(=O)R⁹, -C(=O)OR⁹, -C(=S)R⁹, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl, -CO₂R¹⁸, NO₂, -NR⁷R⁸, C_{1-18} haloalkyl, C(=O)R¹⁸, C(=S)R¹⁸, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19} ;

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, -C(=O)R¹²; -C(=S)R¹², an amino

acid residue linked through a carboxyl group thereof, or where R^7 and R^8 together with the nitrogen form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, $-NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, or $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, or an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{17} is independently selected from the group consisting of (a) hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halogenated alkyl, C_{2-18} halogenated alkenyl, C_{2-18} halogenated alkynyl, C_{1-18} halogenated alkoxy, C_{1-18} halogenated alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, CO_2H , CO_2R^{18} , NO_2 , NR^7R^8 , haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, heterocycle, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle and C_{1-18} hydroxyalkyl, where each of said aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle, or C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19} ;

R^{19} is selected from

(a) H;

(b) NO_2 , SH, $NR^{20}R^{21}$, OH, halogen and CN;

(c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20} , $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}=O$, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with $=O$, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, $=O$, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, $=O$, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, or $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH , benzyloxy, and OH; and

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, $(C_{3-10}$ cycloalkyl)- C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl, and salts, tautomers, polymorphs, isomers and solvates thereof.

57. The compound of claim 56 wherein Y is a single bond, and R^1 is aryl.

58. The compound of claim 56 wherein X is C₁-C₁₀ alkylene, C₂₋₁₀ alkenylene or C₂₋₁₀ alkynylene.

5 59. The compound of claim 56 wherein R³ is heterocycle.

60. The compound of claim 56 wherein R³ is heterocycle substituted with R¹⁷ where R¹⁷ is aryl substituted with 1 or 2 R¹⁹.

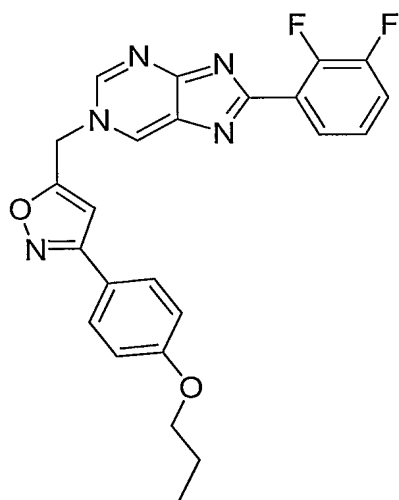
10 61. The compound of claim 56 wherein Y is a single bond, and R¹ is phenyl substituted with 1 or 2 R⁶.

62. The compound of claim 56 wherein R³ is isoxazole substituted with R¹⁷ where R¹⁷ is heterocycle substituted with 1 or 2 R¹⁹.

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63. The compound of claim 60 wherein R¹⁹ is halo or haloalkyl.

64. A compound having the structure



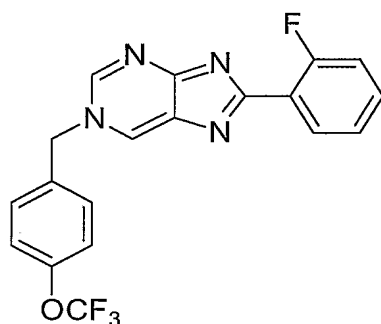
20

and its salts, tautomers, polymorphs and solvates.

65. 8-(2-Fluorophenyl)-1-[(4-trifluoromethyl)phenylmethyl]-1*H*-purine and its salts, tautomers, polymorphs and solvates.

5 66. 1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-8-(2,3-difluorophenyl)-1*H*-purine and its salts, tautomers, polymorphs and solvates.

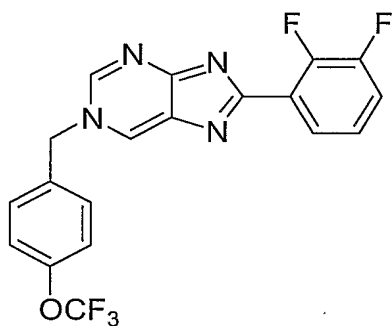
10 67. The compound



and its salts, tautomers, polymorphs and solvates.

15

68. A compound of the structure



20

and its salts, tautomers, polymorphs and solvates.

69. 1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-8-(2,3-difluorophenyl)-1*H*-
25 purine and its salts, tautomers, polymorphs and solvates.

70. A composition comprising a pharmaceutically acceptable excipient and a compound of claims 1, 48, 56, and 64-70.

71. A method comprising administering to a subject in need of treatment or prophylaxis of a viral infection an antivirally effective amount of a composition of claim 70.

72. The method of claim 71, wherein the viral infection is an HCV infection.

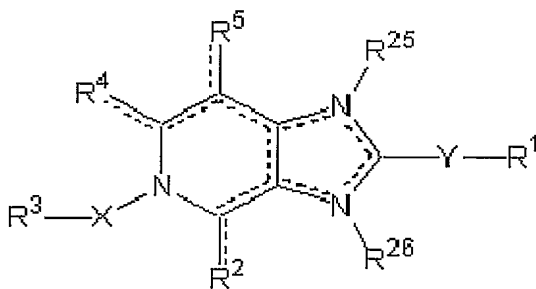
73. The method of claim 72 further comprising administering at least one additional antiviral therapy to the subject.

74. The method of claim 73 wherein the additional therapy is selected from the group consisting of an interferon alpha and ribavirin.

75. A method of screening antiviral compounds which comprises providing a compound of claims 1, 48 or 56 and determining the anti-viral activity of said compound.

76. The method of claim 75 wherein said anti-viral activity is determined by the activity of said compound against one or more viruses belonging to the family of the Flaviviridae and/or of the Picornaviridae.

77. A method for structure-activity determination of analogues of compounds of WO 2004/005286 having the general structure



wherein the R, X and Y groups are defined in WO 2004/005286, comprising

- (A) preparing an analogue of a compound falling within the scope of
WO 2004/005286 wherein C₇ is replaced by N; and
- 5 (B) determining the anti-HCV activity of the compound of step (A).

78. The method of claim 77 wherein the substituent is located at R³, R², R⁴,
R²⁶ and/or R¹.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/026606

A. CLASSIFICATION OF SUBJECT MATTER C07D473/00 C07D471/04 C07D519/00 A61K31/52		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, EMBASE, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15) examples, pages 46-52 and 87-89; page 4, lines 5-18 and pages 119-126 page 87 - page 89; examples -----	56-59, 61
X	EP 1 132 381 A (CERMOL S.A) 12 September 2001 (2001-09-12) example 51 -----	56-58, 61
A	EP 1 162 196 A (JAPAN TOBACCO INC) 12 December 2001 (2001-12-12) abstract; claims ----- -/--	1-78
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search 13 February 2006		Date of mailing of the international search report 01/03/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Frelon, D

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/026606

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/20400 A (AXYS PHARMACEUTICALS, INC; HATAYE, JASON, M; RICE, KENNETH; SHELTON, E) 13 April 2000 (2000-04-13) page 1; claims -----	1-78
A	WO 95/02597 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 26 January 1995 (1995-01-26) abstract; claims -----	1-78
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A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" XP002367158 retrieved from STN Database accession no. 1989:165603 abstract & KHIMIKO-FARMATSEVTICHESKII ZHURNAL, vol. 23, no. 1, 1989, pages 56-59, -----	1-78
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/026606

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 71-74 and 75-78 are directed to a method of treatment of the human/animal body and/or to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/026606

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/026606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2005063744	A	14-07-2005	NONE

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 June 2006 (29.06.2006)

PCT

(10) International Publication Number
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C07D 471/04 (2006.01) **A61P 31/12** (2006.01)
A61K 31/437 (2006.01)

(21) International Application Number:
PCT/US2005/046477

(22) International Filing Date:
21 December 2005 (21.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/638,215 21 December 2004 (21.12.2004) US

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(72) Inventors; and

(75) Inventors/Applicants (for US only): **BONDY, Steven, S.** [US/US]; 95 Hillview Drive, Danville, CA 94506 (US). **OARE, David, A.** [US/US]; 1622 Ralston Avenue, Belmont, CA 94002 (US). **TSE, Winston, C.** [US/US]; 1128 Shoreline Drive, San Mateo, CA 94404 (US).

(74) Agents: **KUTZENCO, Allan, N.** et al.; GILEAD SCIENCES, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(81) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
10 August 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZO[4,5-C]PYRIDINE COMPOUND AND METHOD OF ANTIVIRAL TREATMENT

(57) Abstract: The compound 5-((3-(2, 4-trifluoromethylphenyl)isoxazol-5-yl)methyl)-2-(25 fluorophenyl)-5H-imidazo[4,5-c]pyridine, together with the salts and solvates thereof. Also provided are compositions comprising this compound and pharmaceutically acceptable carriers, as well as the use of such compositions in the treatment or prophylaxis of viral infections.



WO 2006/069193 A3

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/046477

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 A61K31/437 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15) the whole document	1-5
P,X	WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005 (2005-07-14) abstract; example 6	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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Stroeter, T

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/046477

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3 and 4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/046477

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004005286 A	15-01-2004	AU 2003243846 A1	23-01-2004
		BR 0312547 A	26-04-2005
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		US 2005239821 A1	27-10-2005

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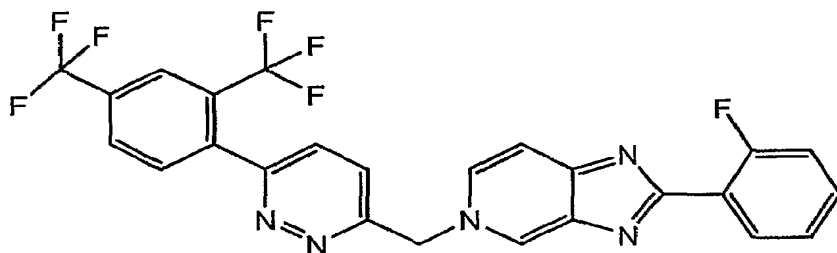
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(54) Title: NOVEL PYRIDAZINE COMPOUND AND USE THEREOF



(1)

(57) Abstract: A compound of formula (1) and its salts and solvates are provided for the treatment or prophylaxis of hepatitis C virus infections (1) Methods of making and formulating compound (1) are provided.

NOVEL PYRIDAZINE COMPOUND AND USE THEREOF

Background of the Invention

The hepatitis C virus is an enveloped, single-stranded, positive sense RNA virus in the family *Flaviviridae*. HCV mainly replicates within hepatocytes in the liver. Circulating HCV particles bind to receptors on the surfaces of hepatocytes and subsequently enter the cells. Once inside the hepatocyte, HCV utilizes the intracellular machinery necessary to accomplish its own replication. Lindenbach, B. *Nature* 436(7053):932-8 (2005). The HCV genome is translated to produce a single protein of around 3011 amino acids. This "polyprotein" is then proteolytically processed by viral and cellular proteases to produce three structural (virion-associated) and seven nonstructural (NS) proteins.

HCV encodes two proteases, the NS2 cysteine autoprotease and the NS3-4A serine protease. The NS proteins then recruit the viral genome into an RNA replication complex, which is associated with rearranged cytoplasmic membranes. RNA replication takes place via the viral RNA-dependent RNA polymerase of NS5B, which produces a negative-strand RNA intermediate. The negative strand RNA then serves as a template for the production of new positive-strand viral genomes. Nascent genomes can then be translated, further

replicated, or packaged within new virus particles. New virus particles presumably bud into the secretory pathway and are released at the cell surface.

HCV has a high rate of replication with approximately one trillion particles produced each day in an infected individual. Due to lack of proofreading by the HCV RNA polymerase, HCV also has an exceptionally high mutation rate, a factor that may help it elude the host's immune response.

Based on genetic differences between HCV isolates, the hepatitis C virus species is classified into six genotypes (1-6) with several subtypes within each genotype. Subtypes are further broken down into quasispecies based on their genetic diversity. The preponderance and distribution of HCV genotypes varies globally. For example, in North America genotype 1a predominates followed by 1b, 2a, 2b, and 3a. In Europe genotype 1b is predominant followed by 2a, 2b, 2c, and 3a. Genotypes 4 and 5 are found almost exclusively in Africa. Genotype is clinically important in determining potential response to interferon-based therapy and the required duration of such therapy. Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes (2, 3, 5 and 6). Duration of standard interferon-based therapy for genotypes 1 and 4 is 48 weeks, whereas treatment for genotypes 2 and 3 is completed in 24 weeks.

The World Health Organization estimates that world-wide 170 - 200 million people (3% of the world's population) are chronically infected with HCV. Approximately 75% of these individuals are chronically infected with detectable HCV RNA in their plasma. These chronic carriers are at risk of developing cirrhosis and/or liver cancer. In studies with a 7-16 years follow-up, 7-16 % of the patients developed cirrhosis, 0.7-1.3% developed hepatocellular carcinoma and 1.3-3.7% died of liver-related disease.

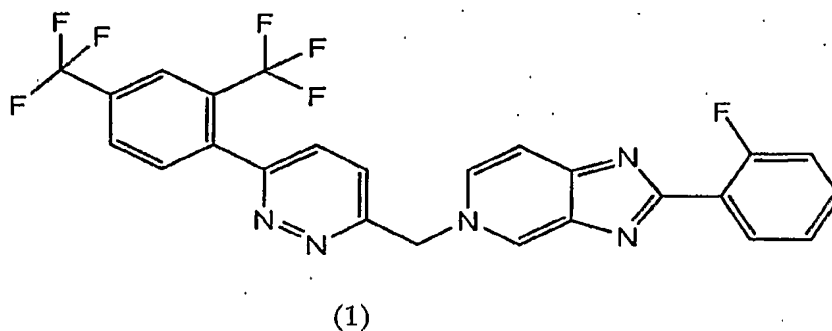
The only treatment option available today is the use of interferon α -2 (or its pegylated form) either alone or combined with ribavirin. However, sustained response is only observed in about 40% of the patients and treatment is associated with serious adverse effects. There is thus an urgent need for potent and selective inhibitors of HCV.

Relevant disclosures include U.S. Patent Nos. 4,914,108; 4,988,707; 4,990,518; 5,137,896; 5,208,242; 5,227,384; 5,302,601; 5,374,638; 5,405,964; 5,438,063; 5,486,525; 6,479,508; and U.S. Patent Publication No. US2003/0108862 A1, Canadian Patent No. 2423800 A1, German Patent Nos. 4211474 A1, 4236026, 4309969, 4318813, European Patent Nos. EP 0 138 552 A2, EP 0 706 795 A2, EP 1 132 381 A1, Great Britain Patent No. 2158440 A, PCT Patent Publication Nos. WO 00/20416, WO 00/39127, WO 00/40583, WO 03/007945 A1, WO 03/010140 A2, WO 03/010141 A2, WO 93/02080, WO 93/14072, WO 96/11192, WO 96/12703, WO 99/27929, PCT-US2004/43112, PCT-BE2003/000117, PCT-US2005/26606, Akamatsu, et al., "New Efficient Route for Solid-Phase Synthesis of Benzimidazole Derivatives", 4:475-483, *J. COMB. CHEM.*, 2002, Baginski SG et al., *Proc. Natl. Acad. Sci. U.S.A.* 2000 Jul 5;97(14):7981-6). Cleve et al., "Derivate des Imidazo[4.5-b]- und Imidazo[4.5-c]pyridins", 747:158-171, *JUSTUS LIEBIGS ANNALEN DER CHEMICA*, 1971, Kiyama, et al., "Synthesis and Evaluation of Novel Nonpeptide Angiotensin II Receptor Antagonists: Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent", 43(3):450-60, *CHEM PHARM BULL*, 1995, Mederski et al., "Synthesis and Structural Assignment of Some N-substituted Imidazopyridine Derivatives", 48(48):10549-58, *TETRAHEDRON*, 1992, Yutilov et al., 23(1):56-9, *KHIMIKO-FARMATSEVTICHESKII ZHURNAL*, 1989. In addition, see WO 05/063744.

A need exists for compounds having desired anti-HCV therapeutic and/or prophylactic attributes, including high potency, selectivity and oral bioavailability (suitable for administration once or twice a day), low toxicity (including acceptable performance in the hERG patch clamp assay, absence of pulmonary permeability edema and no effect on QT interval), minimal or no metabolic activation/glutathione adduct formation, no evidence of genotoxicity, low metabolic turnover and low plasma clearance, wide-spectrum efficacy against HCV genotypes (especially 1a and 1b, 2, 3 and 4), efficacy against HCV resistance mutations (limited overlap in resistance profiles with other non-nucleoside NS5B inhibitors in clinical trials), and compatibility with other HCV therapeutics such as interferon and ribavirin. The safety profile should permit chronic dosing for periods of at least 1 year.

Summary of the Invention

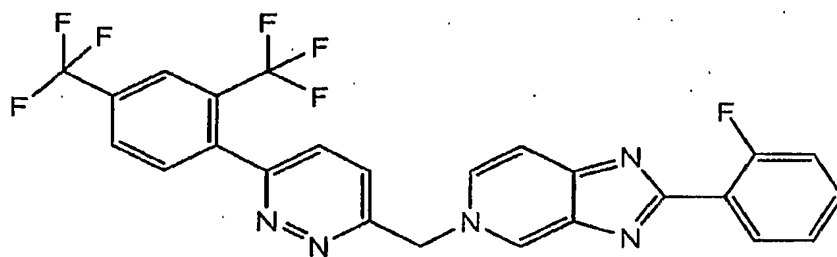
In accordance with achieving the foregoing objects of this invention, a compound is provided having formula (1)



together with its salts and solvates. IUPAC: 5-((6-bis(trifluoromethyl)phenyl)pyridazin-3-yl)methyl)-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine. CAS: 5H-imidazo[4,5-c]pyridine, 5-[[6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl)methyl]-2-(2-fluorophenyl).

Compound (1) is useful in a method for therapy or prophylaxis of HCV infection comprising administering to a subject a therapeutic or prophylactic dose of compound (1). Another embodiment comprises the use of compound (1) for the manufacture of a medicament for the prevention or treatment of a HCV infection in a mammal (more specifically a human).

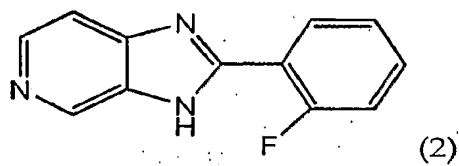
Another embodiment of this invention is a method for making a compound of formula (1)



(1)

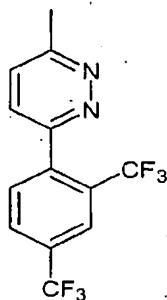
comprising (a) reacting 5-[6-chloro-pyridazin-3-ylmethyl]-2-(2-fluoro-phenyl)-5H-imidazo[4,5-c]pyridine with 2,4-bis(trifluoromethyl)phenylboronic acid in the presence of a solvent having the structure $R^1OR^2O(R^4O)_aR^3$ wherein each of R^1 , R^2 , R^3 and R^4 are independently selected from is C1-C6 alkyl and a is 0 or 1, and (b) recovering compound (1).

In another embodiment for the manufacture of compound (1), a method is provided comprising providing the intermediate (2)



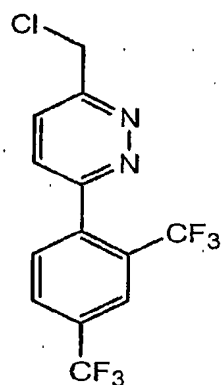
(2)

coupling 2,4-bis(trifluoromethyl)phenylboronic acid to 3-chloro-6-methylpyridazine to produce compound (2a)



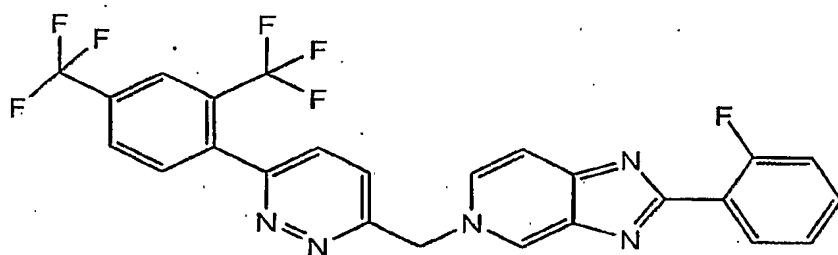
(2a)

treating compound (2a) with a chlorinating agent to produce the alkylating agent (3)



(3)

and using alkylating agent (3) to alkylate intermediate (2) under basic conditions to yield compound (1)



(1)

The alkylating agent (3) is new and is part of this invention, as is the same compound having methyl substitution rather than chloromethyl, or bromo, fluoro or iodo in place of chloro.

Another embodiment of this invention relates to pharmaceutical compositions of the formula (1) compound comprising at least one pharmaceutically acceptable excipient. In one embodiment the compound of formula (1) is formulated with an organic acid and optionally formulated into a

pharmaceutic dosage form such as a capsule. In another embodiment, compound (1) is micronized and formulated as a suspension.

Compound (1) or the pharmaceutical compositions of this invention are employed in the treatment or prophylaxis of hepatitis C.

Figures

Figure 1 depicts an X-ray powder diffraction pattern obtained for crystal form compound (1) reference standard obtained by the method of example 1b.

Figure 2 is an X-ray powder diffraction pattern obtained for amorphous form compound (1) Research Lot 6, obtained by the method of Example 1a.

Figure 3 illustrates a DSC thermogram obtained for crystal form compound (1) reference standard, 1 °C/min scan, obtained by the method of example 1b.

Figure 4 shows a DSC thermogram obtained for amorphous form compound (1) Research Lot 6, 5 °C/min scan, obtained by the method of example 1a.

Detailed Description of the Invention

The therapeutic compound of this invention is administered to a subject mammal (including a human) by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization in a therapeutically effective amount, i.e., an HCV-inhibiting amount or an HCV-replication inhibiting amount. This amount is believed to be an amount that ensures a plasma level of about 100 nM, 3 times the protein adjusted EC₉₀. This ordinarily is expected to be achieved by oral administration of about 0.5 – about 5 mg/kg, typically about 0.7 to 2.2 mg/kg, most ordinarily about 1.2 mg/kg bodyweight for humans.

The optimal dosage of the compound of this invention will depend upon many factors known to the artisan, including bioavailability of the compound in a given formulation, the metabolism and distribution of the compound in the subject, the fasted or fed state of the subject, selection of carriers and excipients in the formulation, and other factors. Proper dosing typically is determined in the preclinical and clinical settings, and is well within the skill of the ordinary artisan. The therapeutically effective amount of the compound of this invention optionally is divided into several sub-units per day or is administered daily or in more than one day intervals, depending upon the nature of the infection, the patient's general condition and the formulation of the compound of this invention. Generally, the compound is administered twice daily.

The compound of this invention is employed in concert with other agents effective against HCV infections. They optionally are administered separately in a course of therapy, or are combined with compound (1) in a unitary dosage form such as tablet, iv solution or capsule. Such other agents include, for instance, interferon-alpha, ribavirin, and/or compounds falling within the disclosures of EP1162196, WO 03/010141, WO 03/007945, WO 00/204425 and/or WO 03/010140 (and other filings within their patent families). Other agents for administration in a course of therapy with the compound of this invention include compounds now in clinical trials, in particular HCV protease inhibitors such as VX-950 (Vertex Pharmaceuticals), SCH 5030347 (Schering Plough) and BILN-2061 (Boehringer Ingelheim), nucleoside HCV inhibitors such as NM283, NM107 (both Idenix/Novartis) and R1626 (Hoffmann-LaRoche), and non-nucleoside HCV inhibitors including HCV-086 and -796 (both ViroPharma/Wyeth). Supplementary antiviral agents are used in conventional amounts, although if the efficacy of the compound of this invention and the supplementary compound are additive then the amounts of each active agent optionally are commensurately reduced, and more so if the agents act

synergistically. In general, however, the agents are used in their ordinary active amounts in unitary combination compositions.

Co-administered agents generally are formulated into unitary compositions with the compound of this invention so long as they are chemically compatible and are intended to be administered by the same route. If not, then they optionally are provided in the form of a medical kit or package containing the two agents in separate repositories or compartments.

The compound of this invention is provided as the free base or as a salt. Salts typically are prepared by acid addition of organic and/or inorganic acids to the free base. Examples include (1) inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and sulfamic acids; or (2) organic acids such as acetic, propanoic, hydroxyacetic, benzoic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, fumaric, tartaric, pyruvic, maleic, malonic, malic, salicylic (e.g. 2-hydroxybenzoic), p-aminosalicylic, isethionic, lactobionic, succinic, oxalic and citric acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, C1-C6 alkylsulfonic, benzenesulfonic, p-toluenesulfonic, and cyclohexanesulfamic acids. Typical salts are the chloride, sulfate, bisulfate, mesylate, besylate, esylate, phosphate, oxalate, maleate, succinate, citrate, malonate, and/or fumarate. Also included within the scope of this invention are the salts of the compound of this invention with one or more amino acids, typically naturally-occurring amino acids such as one of the amino acids found in proteins. The acidic counterion desirably is physiologically innocuous and non-toxic or otherwise pharmaceutically acceptable, unless the salt is being used as an intermediate in preparation of the compounds whereupon toxicity is not relevant. Ordinarily, compound (1) will be administered as the free base, but suitable salts include mesylate (methanesulfonic acid) and HCl.

The compound of this invention includes the solvates formed with the compound of this invention or their salts, such as for example hydrates, alcoholates and the like.

The pharmaceutical compound of this invention optionally is formulated with conventional pharmaceutical carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (2005) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose and/or organic acids such as oleic acid or stearic acid.

The term "pharmaceutically acceptable carrier" as used herein means any material or substance formulated with the active ingredient in order to facilitate its preparation and/or its application or dissemination to the site to be treated. Suitable pharmaceutical carriers for use in the compositions of this invention are well known to those skilled in the art. They include additives such as wetting agents, dispersing agents, adhesives, emulsifying agents, solvents, glidants, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), and isotonic agents (such as sugars or sodium chloride), provided that the same are consistent with pharmaceutical practice, i.e. they are not toxic to mammals.

The pharmaceutical compositions of the present invention are prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients in a one-step or multi-step procedure, with the selected carrier material and, where appropriate, other additives such as

surface-active agents. Compositions containing the compound of this invention formulated into microspheres (usually having a diameter of about 1 to 10 μm) are useful as controlled or sustained release formulations.

In one optional formulation, compound (1) is comminuted to a finely divided form, typically to an average particle size at any point within the range of about 1 - 20 microns. The product of example 1b is crystalline needles and exhibits a range of crystal sizes, typically about 25 – 40 microns. This optionally is micronized in a Jet mill-00 at about 60-80 psi to obtain particles of about 3-4 microns and having surface area of about 7-8 square meters/g. However, the starting crystal sizes will vary from lot to lot and the degree of micronization is a matter of choice. Accordingly, micronized compound (1) is simply defined as crystal or amorphous compound (1) that has been subject to a micronization process such as the exemplary one described here. Neither the size nor surface area of the resulting particles is critical. The micronized compound (1) is suspended in aqueous solution, optionally aided by a suspending agent, emulsifiers and/or surfactant as further described below.

Typically, the pharmaceutical formulation is a solubilized form of compound (1) where compound (1) is dissolved in an appropriate solvent or solubilizing agent, or combinations thereof. Compound (1) solubilized in organic solvent is useful as an intermediate for the preparation of crystalline compound (1), but typically it is solubilized in a pharmaceutically acceptable excipient for administration therapeutically or prophylactically.

Suitable solutions of compound (1) for pharmaceutical preparations include water together with various organic acids (typically C₄ – C₂₄) usually fatty acids like capric, oleic, lauric, capric, palmitic and/or myristic acid. The fatty acids are optionally saturated or unsaturated, or mixtures thereof. In addition, polyethylene glycols (PEGs) and/or short, medium, or long chain mono, di, or triglycerides are employed supplementary to, or in place of, the

organic acids. Pegylated short, medium or long chain fatty acids optionally also are used in the same fashion.

The most common organic acids are the carboxylic acids whose acidity is associated with the carboxyl group -COOH . Sulfonic acids, containing the group OSO_3H , are relatively stronger acids for use herein. In general, the acid desirably contains a lipophilic domain. Mono- or di-carboxylic acids are suitable.

Suitable surface-active agents optionally are used with any of the formulations of this invention (any one or more of the following agents, typically any one of them). Such agents also are known as emulgents or emulsifiers, and are useful in the pharmaceutical compositions of the present invention. They are non-ionic, cationic and/or anionic materials having suitable emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids ($\text{C}_{10}\text{-C}_{22}$), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable from coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms.

Examples of alkylarylsulphonates are the sodium, calcium or alcoholamine salts of dodecylbenzene sulphonic acid or dibutyl-naphthalenesulphonic acid or a naphthalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphosphatidyl-choline and their mixtures. Aqueous emulsions with such agents are within the scope of this invention.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol -polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol,

polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C8 - C22 alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl and oleyl) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose is found in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Corp., Ridgewood, New Jersey, 1981), "Tensid-Taschenbuch", 2nd ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants," (Chemical Publishing Co., New York, 1981).

The compound of this invention is administered by any route appropriate to the condition to be treated, such as oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient, but is generally oral.

Formulations of the compound of this invention for oral administration usually are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granular form; as a solution or suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The compound of this invention optionally is presented as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared by compressing in a suitable machine the compound of the invention in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active and/or dispersing agent. Molded tablets typically are made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

The formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the compound is employed with a paraffinic or a water-miscible ointment base. Alternatively, the compound is formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention is constituted from known ingredients in a known manner. While this phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an

oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered by aerosol or powder inhalers, of which numerous examples are available. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

The compound of this invention optionally is formulated into controlled release compositions in which the release of the compound is controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or

toxicity profile of the invention compound. Controlled release compositions are prepared in accord with known methods, many of which involve formulating the active compound with one or more polymer carriers such as polyester, polyamino acid, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymer, methylcellulose, carboxymethylcellulose and/or protamine sulfate. The rate of drug release and duration of action optionally is controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Also suitable are colloid drug delivery systems such as liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition, e.g., tablets, may require protective coatings.

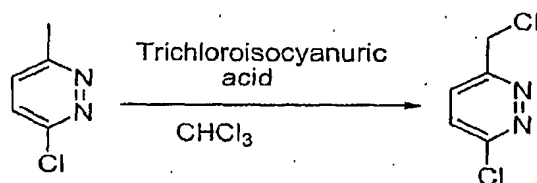
The invention will be more fully appreciated by reference to the following examples, which are to be considered merely illustrative and not limiting the scope of the invention as claimed.

Example 1a

Synthesis of 5-({6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl)methyl}-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine.

In this method, dimethoxyethane or its related solvents, all having the general formula $R^1OR^2O(R^4O)_aR^3$ wherein each of R^1 , R^2 , R^3 and R^4 are independently selected from C1-C6 alkyl and a is 0 or 1, have been found to be particularly advantageous over the conventional solvent DMF. Typically, each of R^1 , R^2 , R^3 and R^4 are independently C1-C2 alkyl and usually a is 0. C1-C6 alkyl includes fully saturated primary, secondary or tertiary hydrocarbon groups with 1 to 6 carbon atoms and thereby includes, but is not limited to methyl, ethyl, propyl, butyl, etc.

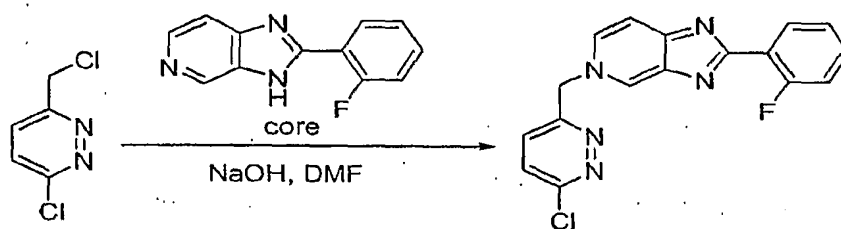
Step 1



Compound	MW	Amount	mmoles	Equivalents
SM	128.56	5 g	38.9	1
TCCA	232.41	3.62 g	15.6	0.4
CHCl_3		130 ml		

To a solution of the commercially available starting material (SM) in CHCl_3 , trichloroisocyanuric acid (TCCA) was added at 60°C . Then the solution was stirred for 1.5 hrs., cooled down and filtered with HiFlo-Celite. The filtrate was concentrated and dried with vacuum. The yield was 5.037 g.

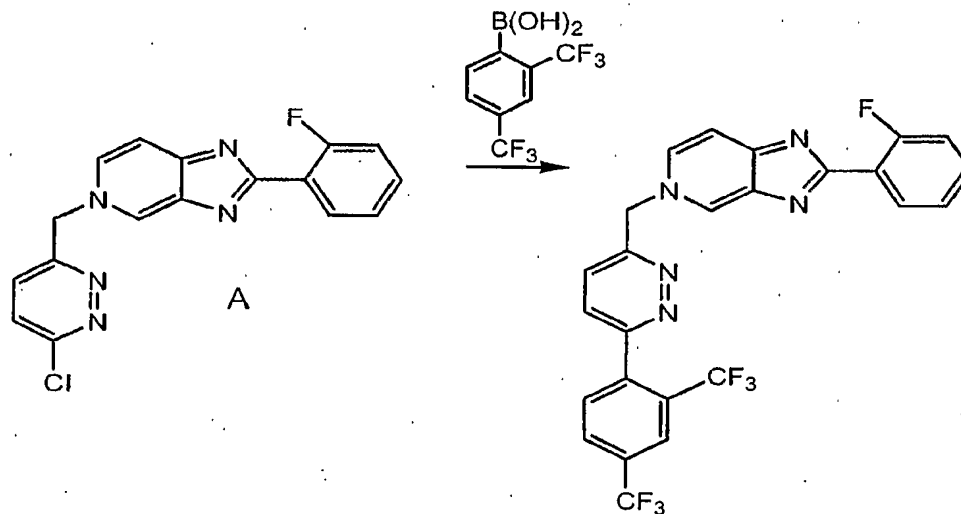
Step 2



Compound	MW	Amount	mmoles	Equivalents
S.M.	163	5.073 g	31.12	1
Core	213.2	6.635 g	31.12	1
NaOH (10%)	40	1.245 g	31.12	1
DMF		320 ml		

To a solution of core (obtained as described in literature in DMF (dimethylformamide), NaOH was added. Then SM for this step (obtained from step 1) was dissolved in DMF (20 ml) and added to the solution slowly. The reaction was stirred for 3 hrs, was diluted with water and extracted with EtOAc. The organic layer was dried with Na₂SO₄. The solvent was removed and the product recrystallized with DCM (dichloromethane). The yield was 5.7 g.

Step 3



Compound	MW	Amount	Moles	Equivalents
A	453.79	95mg	0.209	1
DME	500ul			
2N aq. Na ₂ CO ₃		313ul	0.626	3
2,4-bisCF ₃ -phenylboronic acid	257.93	80.9mg	0.313	1.5
Pd(PPh ₃) ₄	1155	12mg	0.0104	0.05

Compound A was dissolved in dimethoxyethane (DME). To this solution was added 2,4-bis(trifluoromethyl)phenylboronic acid and a 2N aq. Na₂CO₃ solution. To the resulting biphasic mixture was added Pd(PPh₃)₄ and

the reaction was then heated at 80°C for 72 hrs. The reaction was cooled to room temperature and filtered through Celite and the Celite washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified on 6g SiO₂ using MeOH/CH₂Cl₂ to elute compound. The compound thus obtained was contaminated with PPh₃(O). The product was repurified on a 1 mm Chromatotron plate with 0 to 5% MeOH/CH₂Cl₂ in 1% steps. The pure fractions were combined and concentrated in vacuo, then dried on high vacuum for 12 hrs. 11.8 mg of the free base of compound (1) was obtained with no PPh₃ contamination.

¹H NMR (300MHz, CD₃OD)

6.20 (s, 2)

7.32 (m, 3)

7.52 (m, 1)

7.78 (d, 1)

7.89 (d, 1)

7.95 (s, 2)

8.15 (m, 3)

8.35 (d, 1)

9.12 (s, 1)

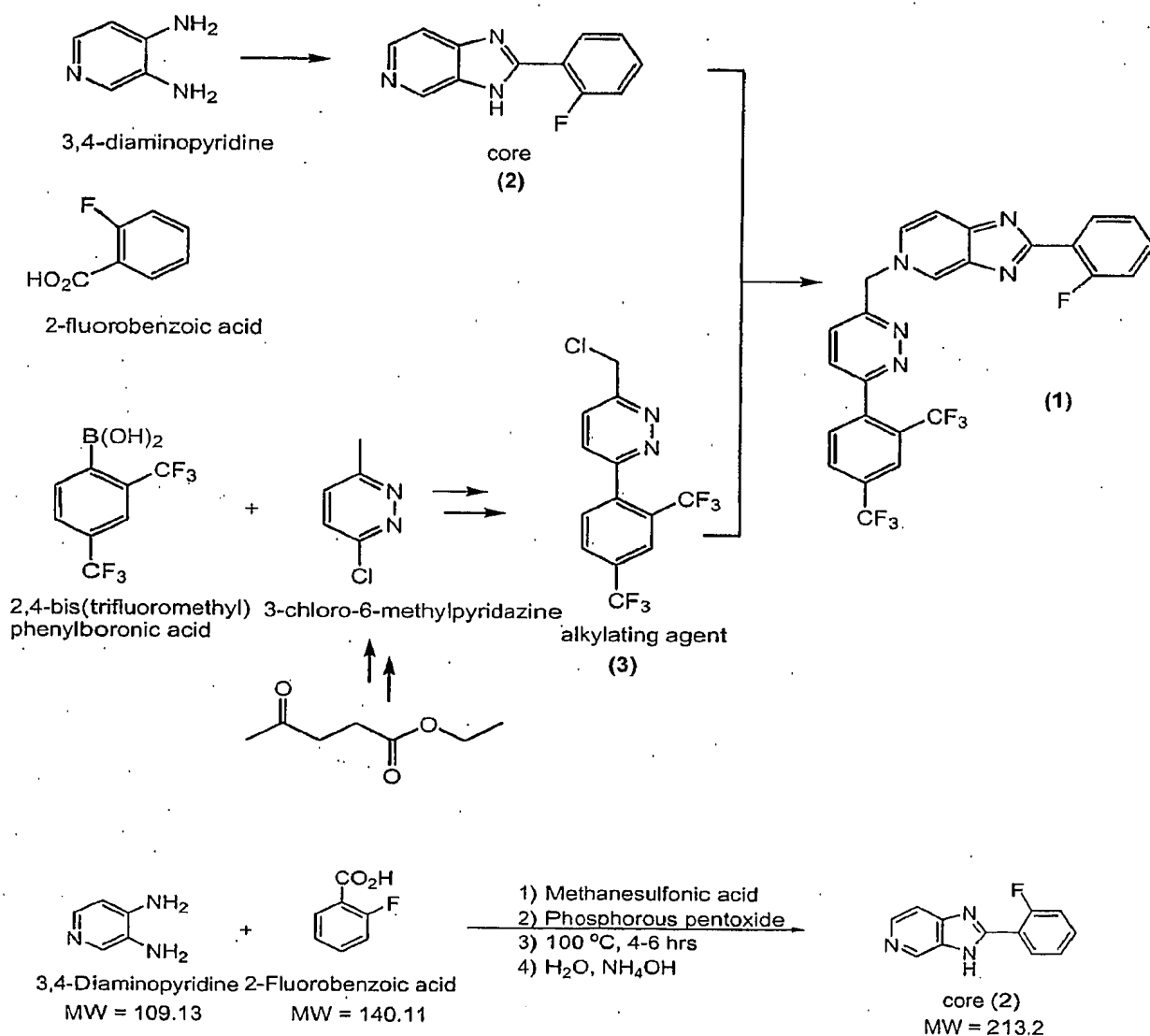
LC/MS M+H = 518

Example 1b

Synthesis of 5-([6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl]methyl)-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine

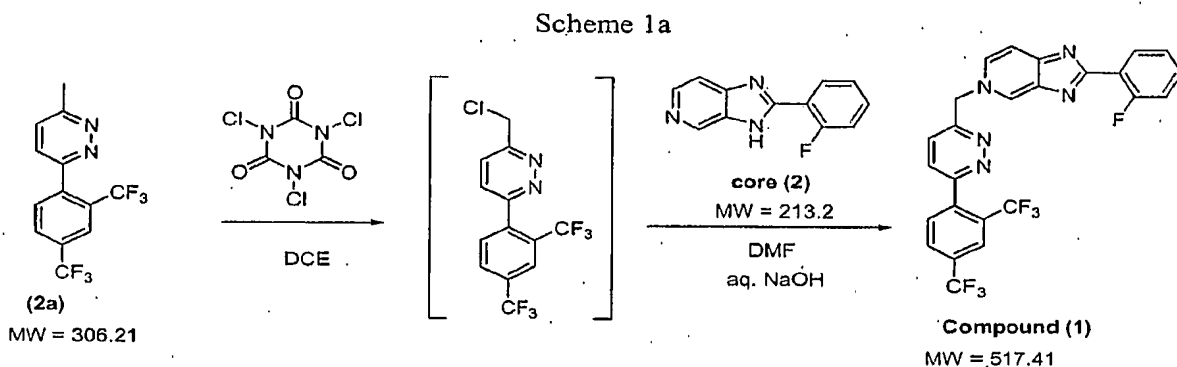
This example is directed to an additional method for making compound (1), employing the following schemes.

Scheme 1



Methanesulfonic acid was added to 2-fluorobenzoic acid in a reactor with active cooling keeping $T \leq 50^{\circ}\text{C}$. 3,4-Diaminopyridine was then added portionwise to this cooled slurry, keeping $T \leq 35^{\circ}\text{C}$. The contents of the reactor were then heated to 50°C . Phosphorus pentoxide was added in a single charge. The reaction was then heated at $90\text{--}110^{\circ}\text{C}$ for at least 3 hours. The reaction was sampled for completion by HPLC analysis. The reaction was cooled to ambient temperature and water was added portionwise slowly to quench the reaction. The reaction was then diluted with water. Insolubles were removed by filtration. The pH of the filtrate was adjusted to 5.5–5.8 with ammonium hydroxide. The reaction was allowed to self-seed and granulate for ~4 hours at ambient temperature. The pH was then adjusted to 8.0–9.3 with ammonium hydroxide. The slurry was held at ambient temperature for at least 2 hours. The solids were isolated by filtration and washed with water, followed by IPE. The wet cake was dried *in vacuo* at not more than 60°C until $\leq 1\%$ water remains. The dry product is core (2).

Summary of Materials	M.W.	Wt. Ratio	Mole ratio
3,4-Diaminopyridine	109.13	1.0	1.0
2-Fluorobenzoic acid	140.11	1.4	1.1
Methanesulfonic acid	96.1	7.0	8.0
Phosphorus pentoxide	141.94	1.3	1.0
Water	18.02	40	---
Isopropyl ether	102.17	5.0	---
Ammonium hydroxide	35.09	~10	---



A solution of compound (2a) in 1,2-dichloroethane was heated to 40–45°C. Trichloroisocyanuric acid was added and the mixture was heated at 60–70°C for at least 2 hours. The reaction was sampled for completion by HPLC analysis. The reaction was cooled to ambient temperature. Celite was added to absorb insolubles, then solids were removed by filtration. The filtrate was washed with 0.5 N sodium hydroxide solution. The organic layer was concentrated to lowest stirrable volume and displaced with DMF. Core (2) and 10% aqueous sodium hydroxide solution were added. The reaction was stirred at ambient temperature for at least 8 hours. The reaction was sampled for completion by HPLC analysis. An additional 10% charge of 10% sodium hydroxide solution was added to the reaction. The reaction was then charged into water to isolate the crude product. After granulating for at least 1 hour, the solids were isolated and washed with water and isopropyl ether. Ethyl acetate was added and refluxed (internal T = 70–77 °C) for 1–5 hours to dissolve product, then cooled to 18–23 °C slowly over 4–8 hours. The reactor contents were agitated at 18–23 °C for 8–20 hours and solids collected by filtration and rinsed with ethyl acetate. Low melt (i.e., DSC about 220 degrees C) amorphous compound (1) was discharged. Amorphous compound (1) was dissolved in ethyl acetate by heating at reflux (internal T = 70–77 °C) for 1–5 hours. Water content is controlled to about 0.2% by azeotropically removing water (with

ethyl acetate the upper limit on water content is about 0.6% by weight; at about 0.9% by weight water the amorphous material will reprecipitate and crystals will not be obtained). The reactor contents are cooled slowly to 18–23 °C over 4–8 hours, then agitated at 18–23 °C for 8–20 hours and solids collected by filtration. The solids were rinsed with ethyl acetate and dried *in vacuo* at not more than 60°C to obtain the dry crystalline compound (1).

Summary of Materials	M.W.	Wt. Ratio	Mole ratio
3-chloro-6-methylpyridazine	128.56	1.0	1.0
2,4bis(trifluoromethyl)phenylboronic acid	257.93	4.0	2.0
X-Phos	476.72	0.18	0.05
Palladium acetate	224.49	0.04	0.025
1,2-Dimethoxyethane	90.12	16.7	---
Potassium carbonate	138.21	2.15	2.0
Water	18.02	7.8	---
Copper iodide	190.45	0.037	0.025
Celite	---	0.25	---
Heptane	100.2	22.4	---

Nuclear Magnetic Resonance (¹H-, ¹³C-, and ¹⁹F-NMR) Spectra

Nuclear magnetic resonance (NMR) spectra of compound (1) is consistent with the proposed structure. The ¹³C, ¹⁹F, and ¹H-NMR spectra of compound (1) in DMSO-d₆ were measured using a Varian UnityInova-400 FT-NMR spectrometer. Spectra are shown in the table below. The NMR chemical shift assignments were established using 2D correlation experiments (COSY, HSQC, HMBC and HSQCTOCSY).

¹H- and ¹³C-NMR chemical shift assignments for Compound (1) reference standard

Atom	$\delta\text{C/ppm (DMSO-}d_6\text{)}$	$\delta\text{F/ppm (DMSO-}d_6\text{)}$	$\delta\text{H/ppm (DMSO-}d_6\text{)}$
1A	140.16		
2A	128.32 (q ^a , $J_{\text{CF}} = 32$ Hz)		
3A	123.61, m		8.24 (m, 1 H)
4A	130.27 (q, $J_{\text{CF}} = 34$ Hz)		
5A	129.54 (q, $J_{\text{CF}} = 3$ Hz)		8.22 (m, 1 H)
6A	133.36		7.88 (m, 1 H)
7A	123.20 (q, $J_{\text{CF}} = 273$ Hz)	-56.4 ^b	
8A	123.02 (q, $J_{\text{CF}} = 275$ Hz)	-62.0 ^b	
1B	158.76		
2B	128.16		8.01 (d, 1 H, $J = 8.4$ Hz)
3B	126.20		7.95 (d, 1 H, $J = 8.8$ Hz)
4B	157.70		
5B	60.49		6.17 (s, 2 H)
2C	131.86		8.31 (m, 1 H)
3C	112.63		7.86 (m, 1 H)
4C	155.44		
6C	168.11 (d, $J_{\text{CF}} = 6$ Hz)		
8C	145.08		
9C	133.06		9.25 (s, 1 H)
1D	123.11 (d, $J_{\text{CF}} = 10$ Hz)		
2D	160.46 (d, $J_{\text{CF}} = 254$ Hz)	-111.7	
3D	116.59 (d, $J_{\text{CF}} = 22$ Hz)		7.29 (m, 1 H)
4D	130.84 (d, $J_{\text{CF}} = 8$ Hz)		7.46 (m, 1 H)
5D	124.13 (d, $J_{\text{CF}} = 4$ Hz)		7.31 (m, 1 H)
6D	131.72 (d, $J_{\text{CF}} = 2$ Hz)		8.35 (m, 1 H)

a. multiplicity, s: singlet, d: doublet, q: quartet, m: multiplet

b. interchangeable signals

Differential Scanning Calorimetry

Compound (1) samples made according to the methods of examples 1a (Research lot 6)) and 1b (remaining samples) were subjected to measurement using a Differential Scanning Calorimetry (DSC) apparatus (DSC2010, manufactured by TA Instruments Corporation), under nitrogen atmosphere, sample weight 5 ± 1 mg, temperature rise rate: either 1 °C per min, 5 °C per min or 10 °C per min, open aluminum pan, and indium standard as a reference. The enthalpy, extrapolated onset temperature and apex temperature at an endothermic peak on the obtained DSC curve were determined.

The DSC results for representative Compound (1) batches are summarized in Table 1. When the crystal form of Compound (1) produced by the example 1b method was subjected to DSC scan at 1 °C/min, the enthalpy of the endothermic peak is about $81 \text{ J/g} \pm 1 \text{ J/g}$, and the extrapolated onset temperature is $233.2 \text{ °C} \pm 2.0 \text{ °C}$. The apex of the endothermic peak is $233.9 \text{ °C} \pm 3.0 \text{ °C}$.

Table 1. Example DSC values obtained for Compound (1) batches

	10 °C/min scan		1 °C/min scan		
	peak onset	main peak	peak onset	main peak	Enthalpy (J/g)
compound (1) Ref Std	235.8	237.2	233.7	234.6	89.5
compound (1)-A-1	n/a	n/a	234.8	234.0	--
compound (1)-B-1 Crop 1	235.2	237.4	231.6	232.2	78.5
compound (1)-B-1 Crop 2	236.1	238.5	234.3	235.6	80.9
**Research Lot 6	220.2	221.3	pending	pending	39.1

Note: All °C except for enthalpy

**5 °C/min scan reported for Lot 6

X-Ray Powder Diffractometry

Samples made by methods 1a and 1b were analyzed in the as received condition, only mixing with a spatula prior to analysis. A sample was fixed to an aluminum cell, and the measurement was performed using an X-ray powder diffractometer (XRD-6000, Shimadzu Lab X, manufactured by Shimadzu Corporation, X-ray source: Cu—K α 1 ray, tube voltage: 35 kV, tube electric current: 40 mA, scan speed: 2° per min, continuous scan mode, sampling pitch: 0.02°, scan range: 4 – 35°, β axis rotation: 60 rpm).

Non-micronized, ascicular compound (1) crystals obtained by the example 1b method have an X-ray powder diffraction pattern having characteristic diffraction peaks at diffraction angles 2θ (°) of 13.46, 15.59, 16.90, 17.48, 23.05 and 30.15 as measured by X-ray powder diffractometer (Figure 1). Note that the non-micronized “high melt” 235 °C melt ascicular crystal form of compound (1) tested in this example shows some effects due to preferred orientation and particle size. As a result, Figure 1 should be considered merely exemplary because varying the crystal size and orientation will change the magnitude of the peaks in the plot. Additionally, the diffraction peak value at the above mentioned diffraction angle 2θ (°) may show slight measurement error due to the measurement instrument or measurement conditions and the like. Typically, the measurement error generally is within the range of about ± 0.3 . The specification for the Shimadzu XRD-6000 is ± 0.04 . In addition, some variation in peak positions can be expected due to product and experimental variation, so they must be considered approximate.

The 220°C “low melt” solid state form of compound (1) comprised by product made according to the example 1a method (or in the method 1b prior to

the reslurry step) gives an X-ray powder diffraction pattern consistent with amorphous material (Figure 2).

The product of this method 1b is crystalline compound (1) substantially free of amorphous compound. It exhibits an endothermic onset at about 235°C in differential scanning calorimetry (DSC) profile. It exhibits an approximate heat of fusion (ΔH_f) of 81 J/g (42 KJ/mole) \pm 1 J/g. Crystalline compound (1) is produced substantially free of amorphous compound (1) by reslurring the reaction product in substantially anhydrous crystallization solvent, as described above. The crystallization solvent is any solvent or cosolvent mixture in which compound (1) will dissolve. Suitable solvents include isopropyl acetate/ethyl acetate cosolvent, or ethyl acetate alone.

Substantially anhydrous solvent is defined as solvent containing a sufficiently small amount of water that the product compound (1) composition according to method 1b contains crystalline compound (1) and less than about 40%, ordinarily less than about 30, 20, 10, 5, 3, 2 or 1% by weight of any other form of compound (1) (including amorphous compound (1)) in the total of all forms of compound (1) in the product composition.

In general, substantially anhydrous solvent will contain less than about 0.5% - 0.6% by weight of the crystallization solvent as water, although the amount of permitted water will vary based on the objectives of the process. For example, more water can be present if the desired product is permitted to contain the greater proportions of amorphous compound (1). The determination and selection of the amount of permitted water is entirely within the skill of the artisan and will depend upon a number of factors, including the nature and identity of the solvent, the presence of agents for scavenging water, the temperature of the reaction and other conditions.

Compound (1) by example 1b typically exhibits intrinsic solubility of 0.7 micrograms/ml, a pKa of 5.8, log P of 2.8; and geometric mean (3 lots) pH

solubility profile at pH 2 of 458 micrograms/ml and at pH 7.3, 0.7 micrograms/ml. Geometric mean solubility (3 lots) in simulated intestinal fluids (fasted: pH 6.4, 0.75 mM lecithin, 3 mM sodium taurocholate, 270 mOsmol; fed: pH 5.0, 3.75 mM lecithin, 15 mM sodium taurocholate, 635 mOsmol) were 19.1 micrograms/ml (fasted) and 122 micrograms/ml (fed).

Measured parameters vary from lot to lot, so all of the foregoing parameters except molecular weight should be considered to be approximate.

Titration with acids revealed higher solubility with mesylate (>20 mg/ml) compared to the chloride (about 0.6 mg/mL) or sulfate (about 0.5 mg/mL) counterions.

Example 2

Formulation of Compound (1)

Compound (1) formulations are made on a weight by weight basis to achieve 10% w/w active. To make 12 kg solution, exemplary quantitative compositions of compound (1) capsules, 20 mg and 40 mg are listed below.

Quantitative composition of Compound (1) capsules, 20 mg and 40 mg

Components	% w/w	Capsule Unit Formula (mg/unit)		Compendial Reference	Function
		20 mg	40 mg		
Compound 1	10.00	20.0	40.0	None	Active ingredient
Oleic Acid	84.55	169.1	338.2	NF	Solvent
Polysorbate 80	5.00	10.0	20.0	NF	Surfactant
Butylated Hydroxytoluene (BHT)	0.10	0.2	0.4	NF	Antioxidant
Butylated Hydroxyanisole	0.35	0.7	1.4	NF	Antioxidant

(BHA)					
Capsule Sealing Solution ^a					Capsule sealant
Ethanol	---	---	---	USP	---
Purified water	---	---	---	USP	---
Capsule Shell, Size 0 Licaps™ White Opaque	N/A	1 each	1 each	None	Capsule shell
Total	100.00	200.0	400.0		

^a Composition is 1:1 w/w ethanol:water solution.

^b Removed during the capsule sealing process.

- Container/vessel: 12kg stainless steel
- Weigh the following in order:
- 0.012 kg butylated hydroxytoluene (0.10%)
- 0.035 kg butylated hydroxyanisole (0.35%)
- 1.2 kg Compound (1) free base (10%).
- 0.6 kg Polysorbate 80 (5%) weighed
- 10.153 kg oleic Acid (equivalent to 84.55 g (84.55%))

Compound (1) capsules, 20 mg or 40 mg, are manufactured through a series of unit process steps. Compound (1) drug substance, oleic acid, polysorbate 80, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA) are mixed until a solution is achieved. The solution is filled into 2-piece hard gelatin capsules. Closed capsules are subsequently sealed with a hydroalcoholic solution, which is evaporated during the sealing process. A vacuum leak test is performed on sealed capsules prior to packaging.

Alternative Formulations

The compound of formula (1) optionally is formulated into a solubilized form with the following agents:

- Fatty acids (short, medium, and long chained as well as saturated and unsaturated), typically C4 to C22. Typical fatty acids are lauric acid, capric acid or oleic acid.
- Alcohols such as ethanol, benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400.
- Surfactants, including both ionic and non-ionic surfactants. Examples of non-ionic surfactants are fatty acid esters of polyoxyethylene sorbitan, sorbitan fatty acid ester, polyoxyethylene castor oil derivatives, polyoxyethyleneglycerol oxystearate, polyethyleneglycol 60, hydrogenated castor oil, and/or block copolymers of ethylene oxide and propylene oxide.
- Antioxidants, for example butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), vitamin E, and/or vitamin E PEG 1000 succinate for chemical stability.
- Viscosity inducer (silicon dioxide, polyethylene glycols, titanium oxide and the like).
- And mixtures of the above

Encapsulation can be performed in a soft elastic gelatin or a hard gelatin or a hard hydroxypropyl methyl cellulose capsule. The liquid formulation (solution or encapsulated solution) provides improved oral bioavailability.

Capsule Filling

The composition and preparation of the soft elastic gelatin capsule is well known in the art. The composition typically comprises from 30-50% by weight

gelatin, 10-40% plasticizer or a blend of plasticizers and about 25-40% by weight water. Plasticizers can be glycerin, sorbitol or sorbitol derivatives, propylene glycol and the like or a combination thereof.

Various methods can be used for manufacturing and filling the soft elastic gelatin capsules such as rotary, liner or accogel machine and the like. Hard gelatin or HPMC capsules can be purchased from Capsugel, Greenwood, S.C. and other suppliers. Capsules are filled manually or by capsule filling machine.

Formulation Preparation

In general, the compositions of this invention can be prepared in the following manner. The ingredients are mixed in an appropriate vessel size using an overhead mixer (The mixing tank may be purged with nitrogen). The pharmaceutically acceptable fatty acid and the pharmaceutically acceptable antioxidant are mixed at room temperature. (The solution may be warmed to appropriate temperature if needed, for example to about 45 degrees C in the case of lauric acid, in order to liquefy the fatty acid). The compound of formula (1) is added and stirred until dissolved. The pharmaceutically acceptable surfactant is added with mixing. The appropriate weight of the resulting mixture is filled into hard gelatin capsules

Additional Formulation Compositions

Formula (1) compound	8.0
PEG 400	82.8
EtOH	9.2
Total	100.0

Formula (1) compound	8.0
EtOH	11.0
PG	7.4
Maisine 35-1	36.8
Cremophor RH40	36.8
Total	100.0

Formula (1) compound	8.0
Oleic Acid	92.0
Total	100.0

Formula (1) compound	8.0
Oleic Acid	73.6
EtOH	9.2
Tween 20	9.2
Total	100.0

Formula (1) compound	8.00%
Oleic Acid	87.40%
Tween 80	4.60%
Total	100.00%

FORMULA (1) COMPOUND	20.00%
Oleic Acid	80.0%
Total	100.0%

FORMULA (1)	20.00%
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COMPOUND	
Oleic Acid	76.00%
Tween 80	4.00%
Total	100.00%

FORMULA (1)	
COMPOUND	8.00
Oleic Acid	86.47%
Tween 80	4.60%
Aerosil 200	0.92%
BHT	0.01%
Total	100.0%

FORMULA (1)	
COMPOUND	8.00
Oleic Acid	85.55%
Tween 80	4.60%
Aerosil 200	1.84%
BHT	0.01%
Total	100.0%

FORMULA (1)	
COMPOUND	8.00
Oleic Acid	85.55%
Tween 80	4.60%
Aerosil 200	1.84%
BHT	0.01%
Total	100.0%

FORMULA (1)	
COMPOUND	10.00
Oleic Acid	84.55%
Tween 80	5.00%
BHA	0.35%
BHT	0.1%
Total	100.0%

Example 2a

Micronized Formulation of Compound (1)

Micronized drug substance (Jet mill-00 at 60-80 psi; 3-4 microns average size, about 7-8 sq. meters/g) was dry blended with lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, tartaric acid, and hydroxypropyl cellulose. The blend was granulated by spraying the blend solution. The granules were dried in a fluid-bed. The dried granules were sized by passing through a mill, and then blended with additional microcrystalline cellulose and croscarmellose sodium. The powder blend was lubricated by adding magnesium stearate and then compressed into tablets using a rotary tablet press. The tablets were subsequently film-coated.

The table below is a summary of various formulations tested in dogs dosed at 40 mg compound (1), corresponding to approximately 4 mg/kg. The table illustrates the superior performance of the solubilized compound (1) formulations.

In-vivo Data Summary

Dosage Form	Process	Formula	Drug Load (%)	C _{max} (μM)	AUC ₂₄ (μM hr)	F (%)	RSD (%)
Solid	Powder Fill ^a	PIC	50	0.7	2.9	8	52
Solubilized	Liquid Fill	Capric acid	20	4.8	25	79	17
		Lauric acid	20	2.6	14.3	44	29
		Oleic Acid	8	3.8	23	67	27
			20	2.1	14	44	56
			25	7.9	42	125	24
Solid	High Shear ^a	SLS only	20	0.4	4.4	13	85
		SLS & Tartaric	20	0.4	2.7	8	82
		SLS & Tartaric ^b	20	0.9	6.9	20	67
	Fluid bed ^a	SLS & Tartaric	20	0.3	4.4	14	77

^a Utilizes micronized API

^b Dosed in dogs treated with pentagastrin to reduce stomach pH

Example 3

Antiviral Activity of Compound (1)

The compound of this invention exhibits anti-HCV replicon activity (assay described in WO 05/063744) against both genotypes 1a and 1b, extremely low cytotoxicity (>50,000 nM in Huh-7, HepG2 and MT4 cells), and a highly favorable selectivity index. The compound is substantially less active against genotype 2a.

Activity of Compound 1 Against HCV Genotype 1b and 1a Replicons

HCV genotype 1b (Con-1/lucneo) and 1a (H77/neo) replicon cells were incubated with serial dilutions of compound (1) 2'-C-methyl adenosine (2'CMeA) or IFNα for 3 days in the absence or presence of 40 mg/mL human serum albumin (HSA). After incubation, replicon RNA levels in the treated cells were determined by either a luciferase reporter assay (1b replicon) or a

quantitative real-time PCR assay (1a replicon) and the data points were used to calculate EC₅₀ (50% effective inhibiting concentration) values for the inhibitors. Compound (1) was shown to inhibit both genotype 1b and genotype 1a replicons with EC₅₀ values of 0.6 and 3.6 nM, respectively (Table A). In the presence of human serum albumin, the EC₅₀ value of Compound (1) was increased to 11 nM.

Table A: Activity of Compound (1) against HCV Genotypes 1a and 1b Replicons

Compound	EC ₅₀ [nM] ^a		
	HCV 1b-lucneo	HCV 1b-lucneo 40 mg/mL HSA	HCV-1a
1	0.6 ± 0.28	11	3.6 ± 1.4
2'CMcA	175 ± 70	250	170
IFN-α	2 IU/mL	n.d.	n.d.

n.d., not determined; HSA, human serum albumin

a Mean EC₅₀ value and standard error determined from at least 4 independent experiments

Activity of Compound (1) Against HCV Genotype 1a Replicon and Virus

The antiviral activity of compound (1) against HCV genotype 2a was tested in cells chronically infected with the genotype 2a virus as well as in cells replicating a subgenomic 2a replicon. Huh-7 cells containing chronically replicating HCV genotype 2a (J6/JFH-Rluc) virus or subgenomic replicons were cultured with compound (1) or 2'CMcA for 3 days in the absence of human serum albumin. After cultivation, the amount of luciferase in 2a-virus containing cells and HCV NS3 protease activity in the 2a replicon-containing cells was determined using Promega's luciferase assay and a novel time-resolved fluorescence assay, respectively.

The antiviral activity of compound (1) was significantly reduced in both the HCV-2a chronically infected cell culture model ($EC_{50} = 2.9 \mu M$) and the 2a subgenomic replicon model ($EC_{50} = 21.9 \mu M$) compared to Huh-7 cells replicating an HCV-1b subgenomic replicon ($EC_{50} = 0.0006 \mu M$) (Table 2). Taken together, these results suggest that the reduction in potency for compound (1) against HCV genotype 2a may be due to the genotypic differences between genotype 1 and genotype 2 of HCV.

Table B: Activity of Compound (1) against HCV Genotypes 1b and 2a

Compound	EC_{50} [nM] ^a		
	HCV 1b-lucneo (subgenomic replicon)	HCV 2a (subgenomic replicon)	HCV-2a (reporter virus)
1	0.6 ± 0.28	21898 ± 18972	2900 ± 1250
2'CMeA	175 ± 70	1610 ± 1099	194 ± 26
IFN- α	2 IU/mL	n.d.	1.2 IU/mL

n.d., not determined; HSA, human serum albumin

a Mean EC_{50} value and standard error determined from at least 4 independent experiments

Compound (1) was evaluated for its cytotoxicity in a variety of cell types including HCV replicon-containing cell lines (Huh-7, SL3 and MH4) and non-replicon-containing cell lines (HepG2, MT4), using a CellTiter-Glo Luminescence Cell Viability assay (Promega). No toxic effects were observed in any of the cell lines at the highest concentration tested ($50 \mu M$) (Table C). These results, coupled with its potent antiviral activity ($EC_{50} = 0.62$ - 3.6 nM) in HCV-1b and HCV-1a replicons, indicates a high selectivity index ($CC_{50}/EC_{50} > 13,000$ - $80,000$) for compound (1).

Table C: Cytotoxicity of compound (1) in HCV Replicon Containing Cell Lines

Compound	CC ₅₀ [μ M] ^a				
	Huh-7 lucneo ^b	SL3 ^b	MH4 ^b	HepG2	MT4
1	> 50	> 50	> 50	> 50	> 50
2'CMeA	7.2 \pm 6	3.9	16	24.3 \pm 2.1	3.5 \pm 1.9

n.d., not determined; HSA, human serum albumin

a Mean CC₅₀ value and standard error determined from at least 4 independent experiments

b HCV replicon-containing cell lines

Anti-HCV Activity of Compound (1) in Combination with IFN In Vitro

Pegylated interferon- α (PEG-IFN- α), in combination with ribavirin, represents the current standard of care for HCV-infected patients. *In vitro* combination studies of compound (1) and IFN- α were performed in replicon cells. Data was analyzed using the MacSynergy template developed by Prichard and Shipman. Results from these studies suggest an additive interaction between compound (1) and IFN- α .

Example 4

Antiviral, Pharmacokinetic and Safety Data for Compound (1) in a Phase-1, First-In-Human Trial in HCV Genotype 1-Infected Subjects.

A randomized, double-blind, placebo controlled trial was designed to evaluate the safety/tolerability, pharmacokinetics and antiviral activity of single (in Part A) and multiple (in Part B) doses of Compound (1) (oleic acid solution, above) in subjects chronically infected with HCV genotype 1 (GT-1) without

decompensated cirrhosis. Prospective subjects are 18-60 years of age, are HCV treatment naïve, and are in general good health.

In completed Part A, five successive cohorts of 6 subjects were randomized (5:1) to receive single ascending doses of Compound 1 (40, 120, 240, 240-with food, or 480 mg) or placebo. In ongoing Part B, four successive cohorts of 12 subjects are randomized (10:2) to receive multiple ascending doses of Compound 1 (40 mg BID, 120 mg BID, 240 mg QD, 240 mg BID) or placebo, over 8 days.

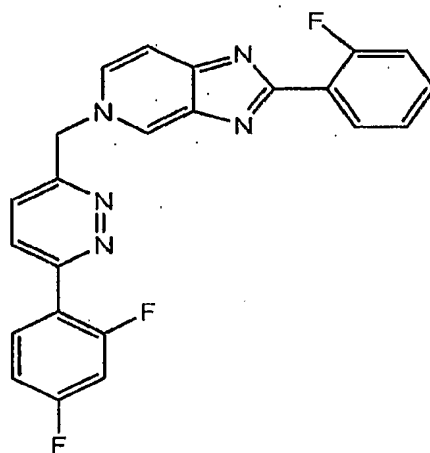
Thirty-one subjects enrolled in Part A were of mean age 43.6 years, predominantly male (20/31), Caucasian (25/31), and infected with either HCV Genotype-1a (24) or 1b (6). Median (range) baseline HCV viral load was 6.6 Log¹⁰ RNA IU/mL (5.2-7.3). Single doses of compound (1) were well tolerated, with no serious or treatment-limiting adverse events (AEs) reported. The most common AE was headache. All AEs were mild in severity, with the exception of one moderate headache. There were no Grade 3 or 4 treatment emergent laboratory abnormalities.

Median compound (1) plasma half-life ranged from 10 to 15 hours across cohorts. Systemic exposure was increased approximately 2-fold when compound (1) was administered with a high fat meal. Mean compound (1) concentration 24 hours after the 240 mg fasted dose dosing was ~7-fold higher than the protein binding adjusted *in vitro* HCV GT-1b Replicon EC₅₀ value. Following single-dose exposure, maximal antiviral effect was observed at 24 hours, with median declines ranging from 0.46 to 1.49 Log¹⁰ HCV RNA IU/mL across cohorts. Individual HCV RNA declines among all compound (1) recipients ranged from 0.19 to 2.54 log¹⁰ IU/mL following single-dose exposure.

This is the first clinical demonstration of antiviral activity of compound (1). Single dose exposure to compound (1) was well tolerated, demonstrated favorable PK properties and potent antiviral activity.

Example 5

The anti-HCV replicon activity of compound (1) was compared to that of a prior art (WO 05/063744) compound, the compound of formula (4)

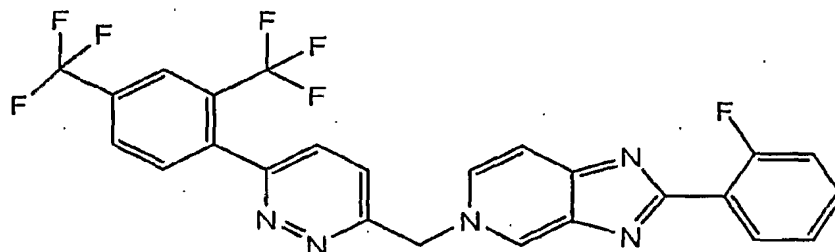


(4)

Unexpectedly compound (1) was about 330 times more potent than the compound of formula (4).

We Claim:

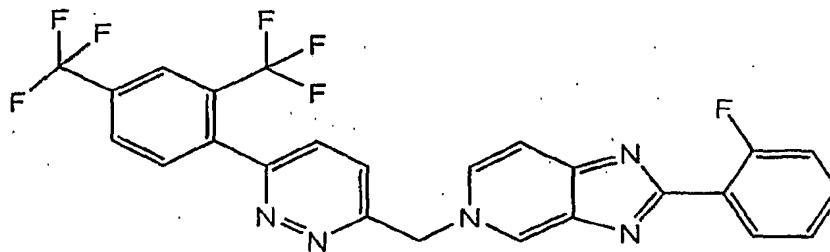
1. A method for making a compound of formula (1)



(1)

comprising (a) reacting 5-[6-chloro-pyridazin-3-ylmethyl]-2-(2-fluoro-phenyl)-5H-imidazo[4,5-c]pyridine with 2,4-bis(trifluoromethyl)phenylboronic acid in the presence of a solvent having the structure $R^1OR^2O(R^4O)_aR^3$ wherein each of R^1 , R^2 , R^3 and R^4 are independently selected from C1-C6 alkyl and a is 0 or 1, and (b) recovering compound (1).

2. The method of claim 1 wherein a is 0.
3. The method of claim 2 wherein the solvent is dimethoxyethane.
4. The method of claim 1 wherein a is 1.
5. A compound having the formula (1)

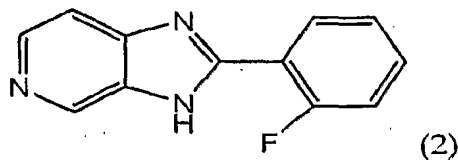


(1)

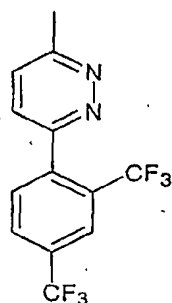
and the salts and solvates thereof.

6. The compound of claim 5 as the free base.
7. The compound of claim 5 which has been micronized.
8. The compound of claim 5 as a suspension.
9. The suspension of claim 5 in an aqueous medium.
10. The compound of claim 5 as a solution.
11. The compound of claim 10 in solution with a C4-C22 fatty acid.
12. The solution of claim 11 wherein the fatty acid is oleic acid or lauric acid.
13. A composition comprising the compound of claim 5 and a pharmaceutically acceptable excipient.
14. The composition of claim 13 wherein the excipient is a C4-C22 fatty acid.
15. The composition of claim 14 which is an aqueous solution and wherein the fatty acid is oleic acid.
16. A method for therapy or prophylaxis of an HCV infection comprising administering to a subject an HCV therapeutic or prophylactic dose of the compound of claim 5.
17. The method of claim 16 wherein the subject is a human.
18. The method of claim 17 further comprising administering to the subject a therapeutically effective dose of another agent for the treatment or prophylaxis of an HCV infection.
19. The method of claim 18 wherein the agent is an interferon.

20. The method of claim 17 wherein the therapeutically effective dose is about from 0.5-5.0 mg/kg BID.
21. The method of claim 20 wherein the dose is about from 0.7-2.2 mg/kg BID.
22. The compound of claim 5 for use as a medicine.
23. The use of the compound of claim 5 for the manufacture of a medicament for the prevention or treatment of an HCV infection in a mammal.
24. The use of claim 23 wherein the viral infection is an infection with HCV.
25. The use of claim 23 wherein the mammal is a human.
26. A method for the preparation of compound (1) comprising providing the intermediate (2)

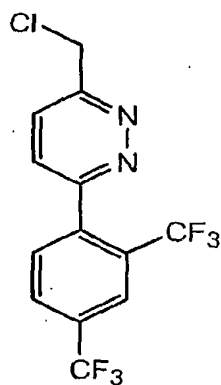


coupling 2,4-bis(trifluoromethyl)phenylboronic acid to 3-chloro-6-methylpyridazine to produce compound (2a)



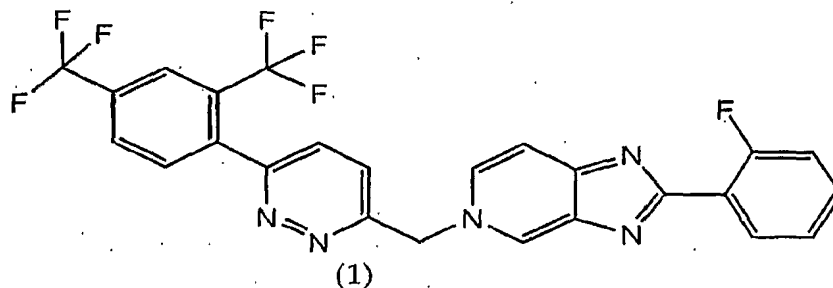
(2a)

treating compound (2a) with a chlorinating agent to produce the alkylating agent (3)

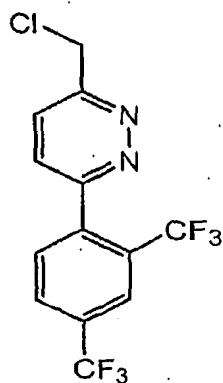


(3)

and using alkylating agent (3) to alkylate intermediate (2) under basic conditions to yield compound (1)



27. A compound of formula (3)



(3)

and its analogues substituted with methyl rather than chloromethyl, and its analogues substituted with bromo, fluoro or iodo in place of chloro.

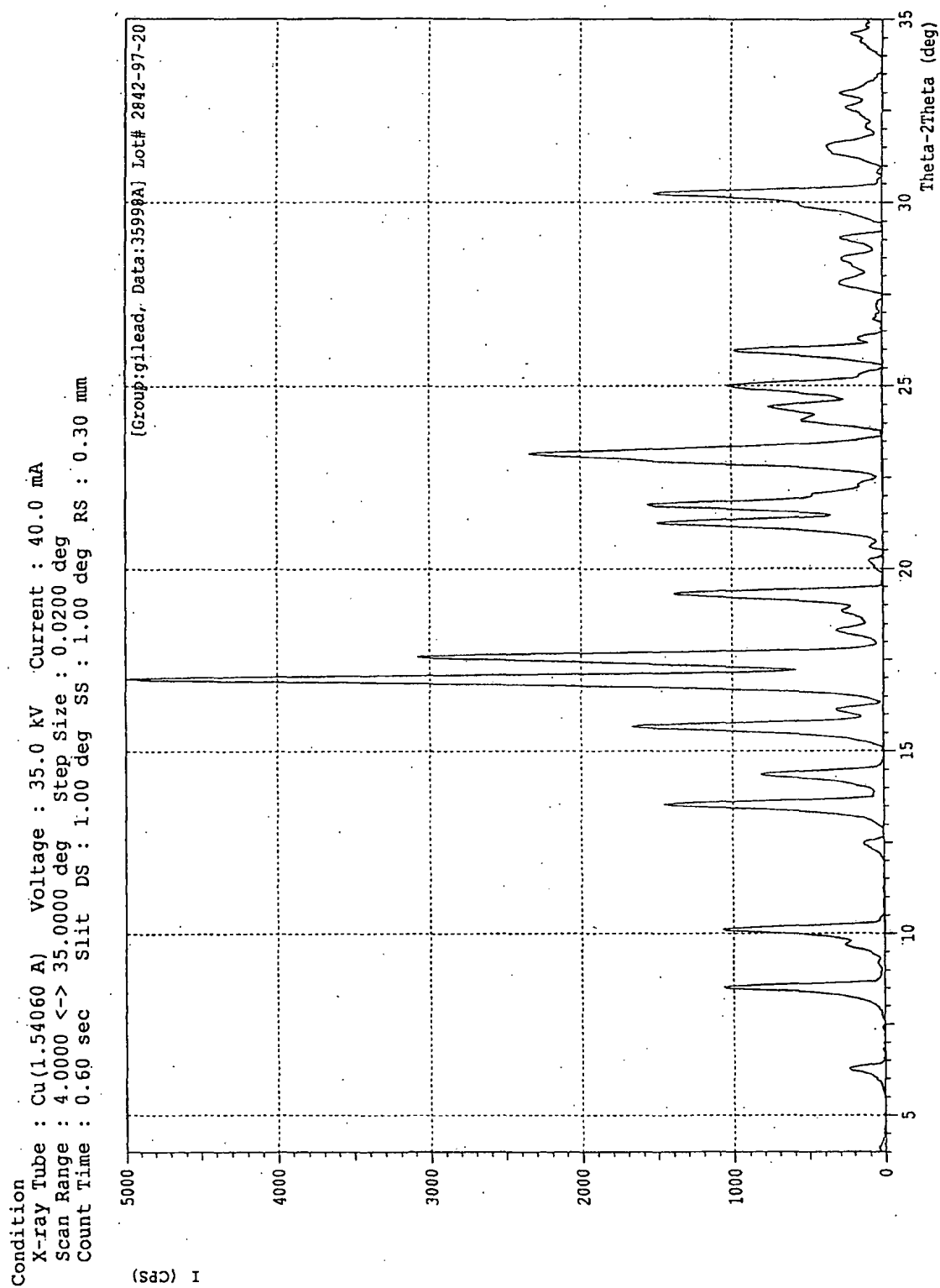


Figure 1/4

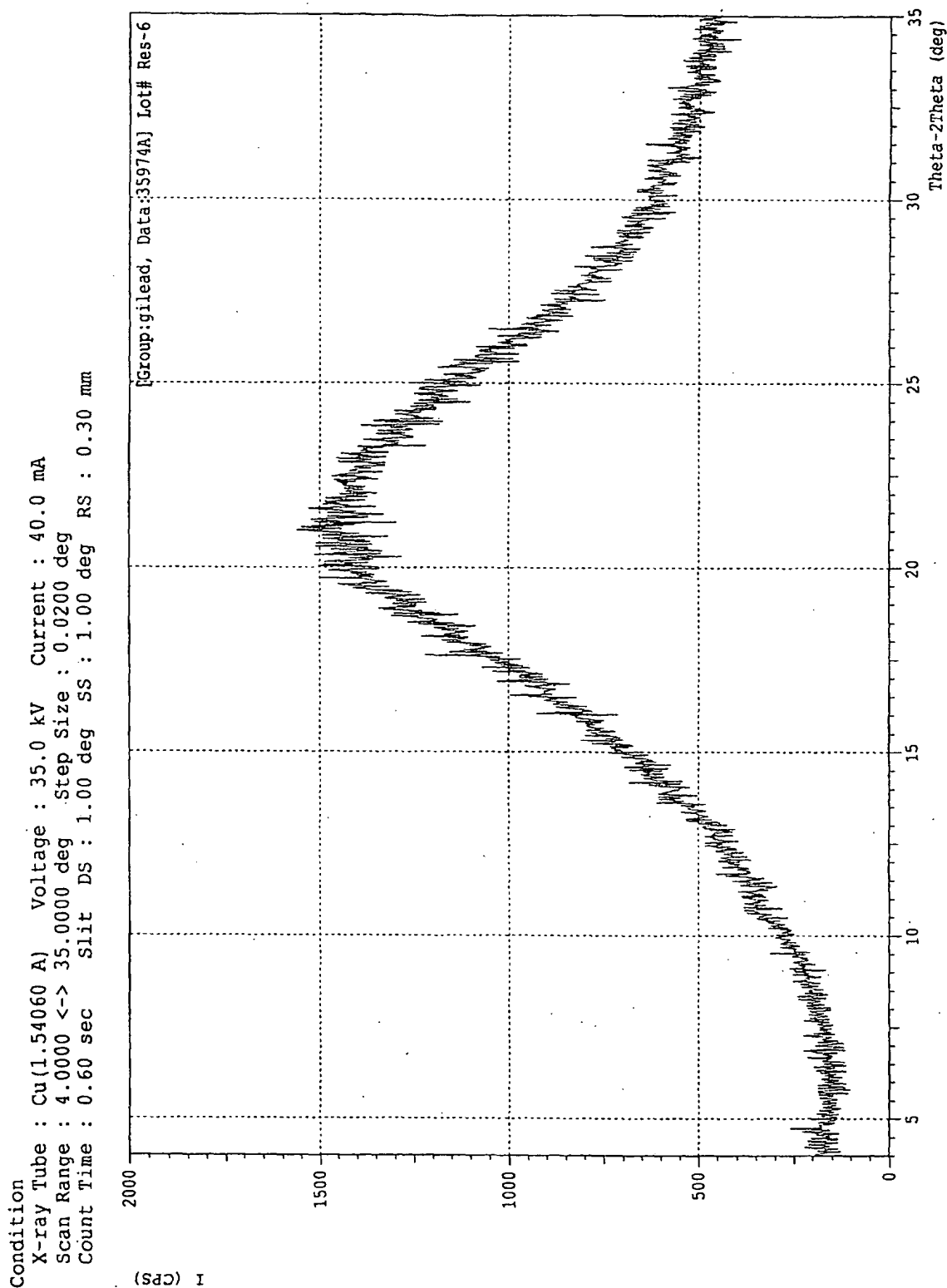


Figure 2/4

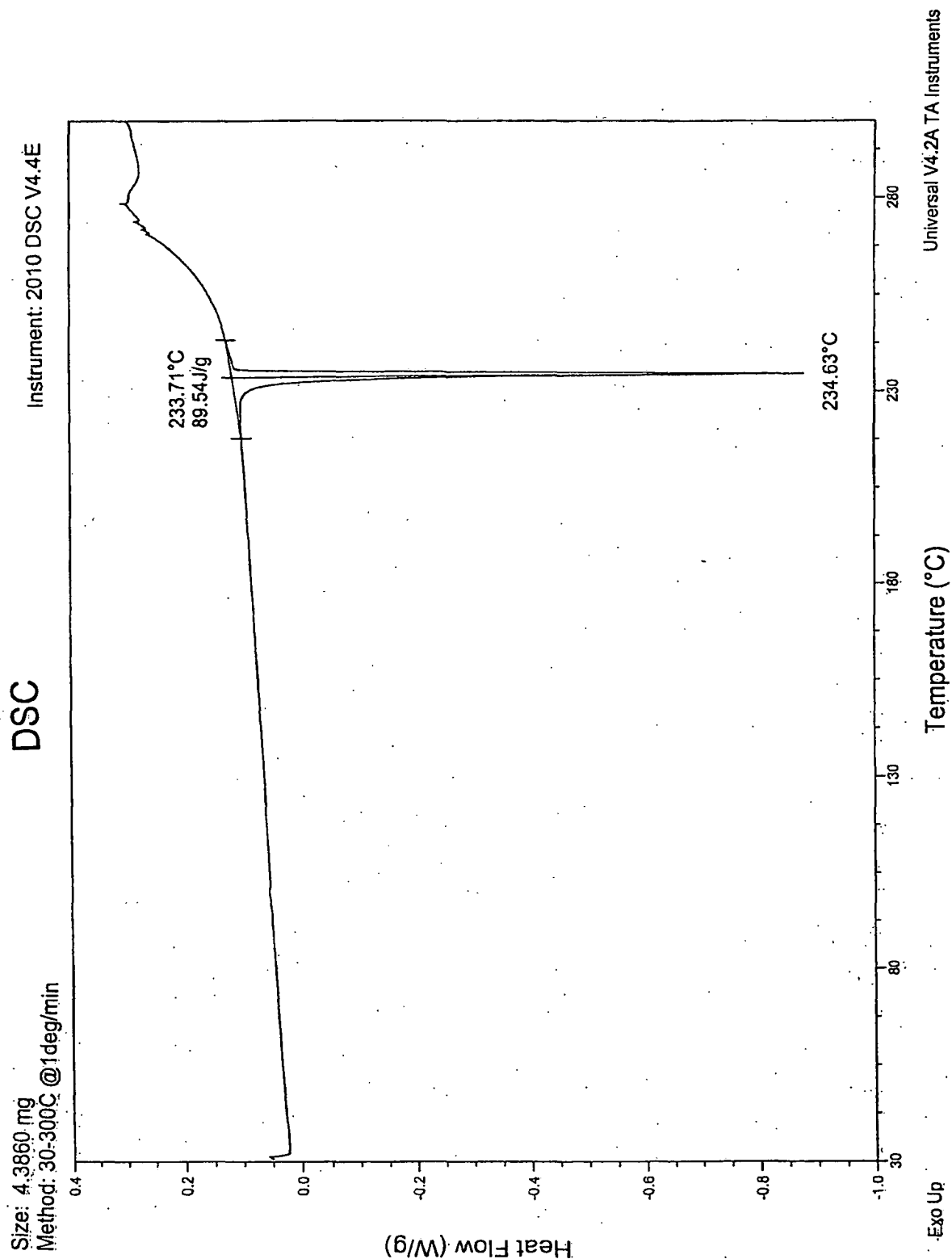


Figure 3/4

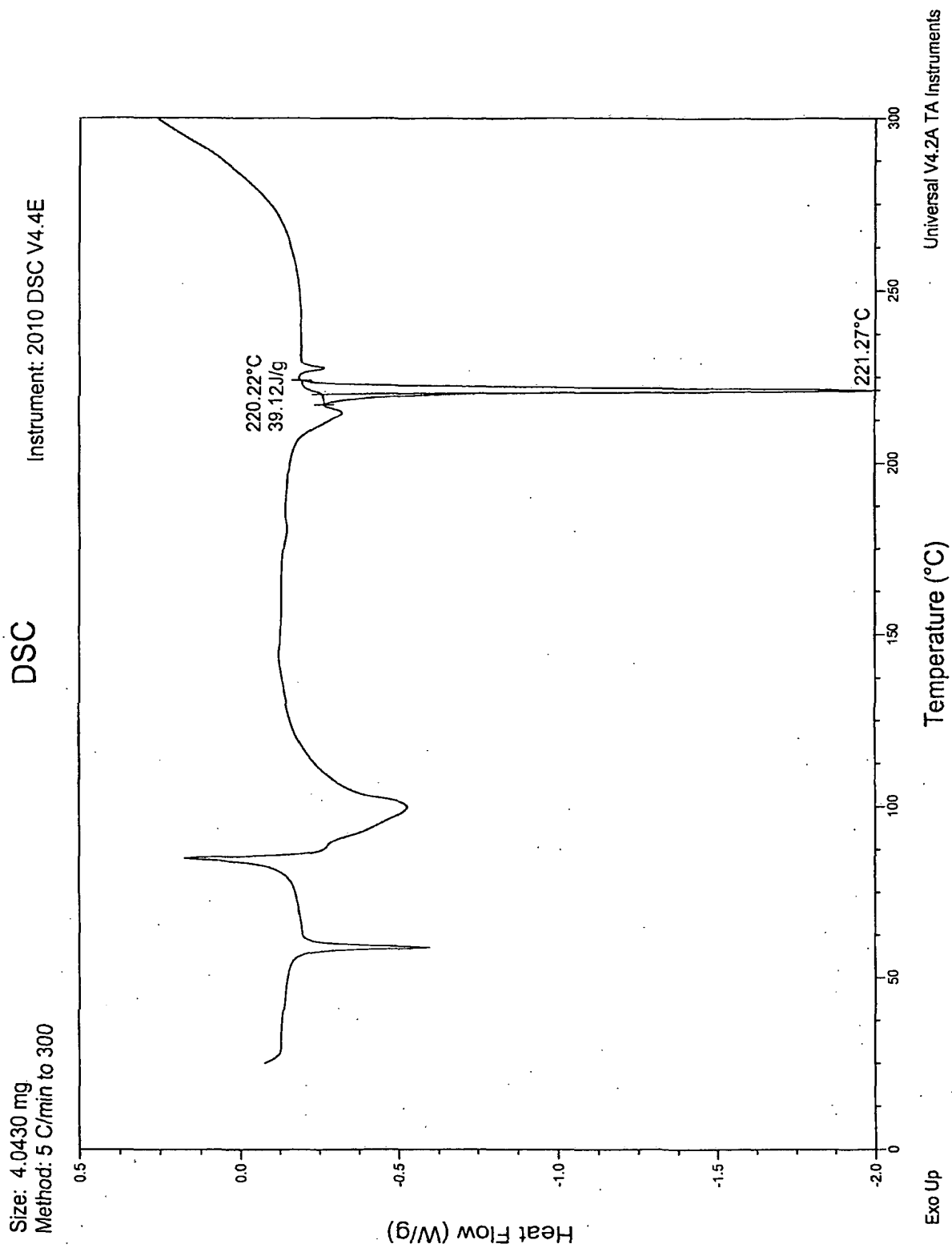


Figure 4/4